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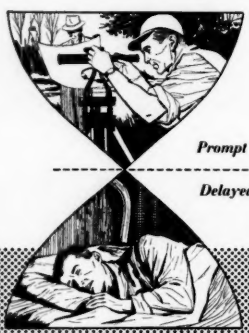

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STUDIES OF THE COMBINED ACTION OF SOME ANTIHISTAMINIC AGENTS

PLUTARCO NARANJO, M.D., and E. BANDA de NARANJO, M.D.
Quito, Ecuador

COMBINATION of two or more pharmacologically related drugs may offer certain advantages over the use of a single drug,[9] such as a higher therapeutic index,[1] faster onset and greater duration of action,[27] extension of the spectrum of therapeutic actions,[29] and supra-additive increase of one or several of the therapeutic effects.[7] The class of antihistaminics, which since its initiation in 1933[8] and first characterization[36] has now grown to include hundreds of representatives,[2,4,11,12,15,25,32,34,35] is an appropriate example of marked differences in pharmacologic properties between the various members of the same class. Whereas they all have in common a certain general selectivity of antihistaminic action, they differ greatly not only in the duration of their antihistaminic action[3,37] but also in the details of antihistaminic activity, such as preventive activity against histamine-produced increase in vascular permeability[13,14] and antagonism against experimental asthma,[2,38] and in the relative intensity of other pharmacologic activities, such as anticholinergic action[5,10,28,40] and potentiation[24] or blockade[17] of adrenergic drugs.

The present study was undertaken in an attempt to answer the question how the pharmacologic properties of individual antihistaminics reappear in the spectrum of action of mixtures composed of two or more of them. For this purpose the investigation was conducted in three sections. Section I dealt with a series of eight common antihistaminics. The major characteristic components of the spectrum of each of them were quantitatively determined; namely, (1) acute toxicity, (2) protection against histamine-induced asthma, (3) protection against lethal effect of intravenous histamine, (4) inhibition of the vasopressor action of histamine,

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(5) inhibition of histamine-induced spasm of isolated ileum and (6) inhibition of acetylcholine spasm of isolated ileum. In Section II, ten binary, eleven ternary and four quaternary combinations were prepared from these eight drugs, and their relative potency against histamine-produced asthma was determined. In Section III, the combination which exhibited the highest degree of anti-asthmatic synergism was studied in greater detail in order to determine to what extent the other pharmacologic properties of this combination parallel the observed increase in anti-asthma potency. For an exhaustive quantitative answer to this question, Section III included an evaluation of the various parameters of selectivity of the combination studied and of the components of the combination.

PROCEDURE AND MATERIALS

1. *Test Substances.*—The following eight antihistaminics were employed: N,N-dimethyl-N′-(4-methoxybenzyl)-N′-(2-pyridyl)-ethylenediamine maleate (Neoantergan), 10-phenothiazinylpropyl-trimethyl-ammonium hydrate (Multergan), 10-(2-dimethylamino-1-propyl)-phenothiazine hydrochloride (Phenergan), N,N-dimethyl-N′-(4-methoxybenzyl)-N′-(2′-pyrimidyl)-ethylenediamine hydrochloride (Neohetramine), 1-(N,N-dimethylamino)-3-(phenyl-3-α-pyridyl)-propane maleate (Trimeton), 2-methyl-9-phenyl-1,2,3,4,-tetrahydro-pyridindene tartrate (Thephorin), N,N-dimethyl-N′-(2-thenyl)-N′-(2-pyridyl)-ethylenediamine hydrochloride (Histadyl) and 2-(N-phenyl-N-benzylaminomethyl)-imidazoline metasulphonate (Antistin). All concentrations are stated in terms of weight of the salt per volume of solvent. Histamine was employed as the biphosphate and acetylcholine as the hydrochloride.

The various mixtures of these eight drugs, employed in the combination studies, are enumerated in Table VIII. One of these mixtures, the ternary combination of 40 per cent of Neoantergan, 30 per cent of Neohetramine and 30 per cent of Trimeton ("Hista-3,15"-Life Laboratories) was chosen for the third section of these studies.

2. *Acute Toxicity.*—The intravenous LD_{50} was determined in guinea pigs, mice and rabbits; single-dose groups of fifteen to thirty-five animals were employed and mean value and "approximate standard error" (s.e.) were calculated graphically by the method of Miller and Tainter.[26]

3. *Antihistaminic Activity.*—Four different parameters of antihistaminic activity were studied by the use of the following test procedures:

(a) *Protective Activity against Histamine Death (Antilethal activity; a).*—This was determined by injecting guinea pigs, two days after histamine pretest in the asthma chamber, intravenously with the antihistaminic and three minutes later with 10 mgm/kg histamine=16 LD_{50}s. Histamine was injected in 0.5 per cent solution. The antihistaminic doses were graded in such a way as to yield data for evaluation, by probit method, of

the PD_{50} for the endpoint selected. By a slight modification of this procedure, namely, by determining several PD_{50} for an entire gradation of endpoints marked by different supra-lethal doses of histamine, the *variation of the lethal dose of histamine with increasing dose of antihistaminic* was studied for an antihistaminic combination, in analogy with investigations of Wells[39] and Lehmann[17] on single antihistamines.

(b) *Protective Activity against Inhalatory Histamine Asthma in the Guinea Pig (Anti-asthma activity; b).*—The method used to produce experimental asthma was essentially the same as described by Loew *et al.*[18] and modified by Siegmund *et al.*[33] Histamine solution (0.5 per cent) was sprayed into an "asthma chamber" by a De Vilbis No. 40 nebulizer under an air pressure of 300 mm Hg. Each animal was first subjected to a pretest to determine the time from the start of histamine inhalation to the onset of convulsions (histamine time, H_t) and to divide the animals, for the protective test, into groups of greatest possible homogeneity as to H_t. At H_t the animals were rapidly removed from the asthma chamber. Fifteen minutes later the antihistaminic test dose was injected subcutaneously, dissolved in the uniform volume of 2 cc solvent per kg body weight, and twenty minutes later the guinea pigs were again exposed to the histamine spray. Graded antihistaminic doses were administered, each to a group of 25 to 125 animals, and the median effective dose (PD_{50}) protecting 50 per cent of animals against convulsions for ten minutes of exposure was determined by the graphical probit method.[26]

(c) *Inhibition of Histamine-Induced Spasm of Isolated Guinea Pig Gut (Antispasmodic Activity; c).*—The antispasmodic effect of the antihistaminics was studied in segments of lower ileum, suspended in 50 cc of Ringer-Locke solution at 30°C, at which temperature[38] the gut is more sensitive to histamine. Antihistamine and histamine were added in a constant volume of 0.1 cc. Washings were made by overflow with 100 cc Ringer-Locke solution. Histamine was employed in the uniform dose of 0.5 μg, which produces a histamine concentration of $1:10^8$ in the bath fluid. Three minutes after a control dose of histamine and subsequent washing, the antihistamine and one minute later histamine were added to the bath, and the percentage difference between the first and the second contraction was measured. From populations of experiments with varied antihistaminic dose the ED_{50} was determined; that is, the dose diminishing by 50 per cent the contractile response to histamine in 50 per cent of experiments.

4. *Anticholinergic Activity (e).*—This was measured by the method described in the preceding section, except that, in the place of histamine, acetylcholine was used. It was also employed in the uniform dose of 0.5 μg, which resulted in a $1:10^8$ concentration in the bath fluid.

5. *Procedures of Evaluation.*—In addition to the D_{50}s, the following two values were determined for all drugs studied: (a) *Potency*, P, referred to

that of Neoantergan=100, was calculated with regard to the various activities studied, in order to facilitate comparisons between the drugs. (b) *Therapeutic Index* (T.I.) (for each activity tested) was calculated as the ratio between LD_{50} in the guinea pig or rabbit and the respective ED_{50}. For evaluation of the drug combinations (m), numerical expressions had to be obtained of their differences in effect from the components. In reference to the intensity of effect, this was accomplished by calculating the "combinatory efficiency" (C.E.),* *i.e.*, the ratio fP/cP—where f stands for "found" and c for "calculated"—between the actual potency of the combination and the potency calculated on the assumption of additive (more precisely: iso-additive;[21,20,23]) behavior of the components. The calculated potency is: $cP=qP_1 + rP_2 + vP_3 + \ldots\ldots$, where $_1$, $_2$, $_3$, *et cetera*, refer to the individual two or more component drugs and 100g 100r, 100v, *et cetera*, indicate their percentage content in combination. Practically, since all D_{50} values required are available, C.E., according to a suggestion of Loewe,[20] is best determined under circumvention of the more complicated calculation of cP on the basis of the fact that P=1/D, hence $C.E.=cD_{50}/fD_{50}$. The value of cD_{50} of the combination (in mgm) is determined (Loewe,[20]) from the equation: $cD_{50}=1/(qD_{50}^{1} + rD_{50}^{2} + vD_{50}^{3} + \ldots\ldots)$. In all cases, N indicates the number of animals or experiments. Under the preceding assumptions, C.E., when 1.0, indicates additive behavior of the combination; when 1.0, supra-additive ("potentiation"), and when 1.0, infra-additive behavior (antagonism). Quite similarly, in reference to margin of safety (T.I.), the efficiency, C.E., of the combination was expressed by the ratio fT.I./cT.I.

The *significance of the difference* between the actual and the calculated D_{50}s for combined effects, expressed in the customary way by the value p for the probability that the difference is due to chance, was calculated with the aid of an appropriately adapted equation for Fisher's t-value:

$$t = \frac{fD_{50} - cD_{50}}{\delta \text{ diff.} \sqrt{{}^{1}/N_m + {}^{1}/N_1 + {}^{1}/N_2 + {}^{1}/N_3 + \ldots\ldots}}$$

On the basis of Miller and Tainter's equation[28] for standard error:

$$\text{s.e.} = \frac{2s}{\sqrt{2N'}}$$

it was assumed that

$$\delta \text{ diff.} = \sqrt{\tfrac{1}{2}[(2s_m)^2/N_m + (2s_1)^2/N_1 + (2s_2)^2/N_2 + (2s_3)^2/N_3 + \ldots\ldots]}$$

where 2s is the increment in dose necessary to raise the probit equivalent of

*"Efficiency" is the English term suggested by Loewe[20] for use in the place of the German term "Variationsgrad" (Loewe,[21]).

TABLE I. ACUTE TOXICITY OF SOME ANTIHISTAMINICS

1	2	3	4	5	6
Drug (intraven.)	LD_{50} (mgm/kgm±s.e.)			Relative Toxicity	References
	Guinea Pig	Mouse	Rabbit		
Trimeton	(25)† 72 ±11	(25) 61.3±8.3	(20) 66±7.1	34	
Phenergan	(28) 42.5± 5	(20) 53.1±6.8	(15) 44±6.3	57.5	
Neohetramine	(25) 38.2±2.8	(15) 42 ±3.7	(14) 46±4	63.9	
Hista-3, 15	(35) 38.0±2.1	(15) 34 ±3.2	(15) 36±4.1	64.2	
Diatrin	30*	45*	30*	81.5	Ercoli et al.,[6]
Thephorin	(20) 24.5±2.7	22.5*	15*	99.9	Lehmann,[17]
Neoantergan	(25) 24.4±3.8	25*	12*	100**	Winter,[41]
Antistin	(15) 17.1±2.2	(15) 20.5±3		142.5	
Benadryl	(15) 16.3±2.1	23*	17*	149.9	Lehmann,[17]
Histadyl	(15) 14.6±2.8	19.8*			Lee et al.,[16]
Pyribenzamine	(15) 11.2±1.6	16*	10*	218	Ercoli et al.,[6]
Multergan	(15) 6.7±0.9	10.2±1.4		376	

†In parentheses, number of animals.
*Values quoted from literature (see column 6).
**Standard of reference.

the number of quantal responses from 4.0 to 6.0 (other symbols are explained above).

Evaluation of Selectivity.—For quantitation of the spectrum of action of individual and combined drugs, the method[19] of determining the *"degrees of relative selectivity"* (D.S.) of the various actions of the same drug was adopted. To obtain sufficiently comparable values for all five activities studied in each drug, the equieffective doses (D_{50}) or concentrations (C_{50}) for the experimentally employed endpoints were converted into those for more uniformly comparable endpoints, namely, of counteraction, on the same median level, of the effect of 1.0 mgm per kgm and ml, respectively, of histamine (effects a to d) or acetylcholine (effect e). Conversion factors employed were 100,000 for activities c and e, 0.1 for activity a, and 5.0 for activity d (see above, sections 2 to 4). For activity b, the factor 2.5 was selected because (1) the endpoint of ten-minute protection employed in all experiments signifies counteraction of four LD_{50}, 2.5 minutes having been found as the mean time interval to inhalatory-histamine death in unprotected animals, and (2) histamine is more effective by inhalation than by the intravenous route. From the converted doses, *relative potencies* (RP) were calculated in reference to the lowest potency found, that of Neohetramine for activity c. By use of the RP values, the *activity type* of each drug included in the comparison and the *level of selectivity* of each of its activities were established and the *degrees of selectivity* (D.S.) for the five activities of each drug as well as the *comparative selectivities* of different drugs in reference to each other were calculated as described by Loewe.[19]

RESULTS AND DISCUSSION

I. Single Antihistaminics

Acute Toxicity.—Results are shown in Table I where the drugs are arranged in ascending order of toxicity (descending order of LD_{50}). For a more complete survey of the acute toxicity of antihistaminics, some ad-

TABLE II. MEDIAN PROTECTIVE DOSE OF SOME ANTIHISTAMINICS AGAINST DEATH FROM INTRAJUGULARLY INJECTED HISTAMINE (10 MGM/KGM)

1	2	3	4	5	6
Drug (intrajugularly)	Number of Animals	PD_{50}		Potency	T.I.
		mgm/kgm	s.e.		
Neoantergan	25	0.0094	0.0011	100.0	2.600
Multergan	20	0.0105	0.0013	89.5	638
Hista-3, 15	35	0.0155	0.0012	60.6	2.450
Phenergan	20	0.0332	0.005	38.5	1.280
Neohetramine	25	0.0678	0.002	13.8	574
Histadyl	20	0.0697	0.005	13.5	210
Trimeton	25	0.0970	0.008	9.4	835
Thephorin	20	0.1017	0.011	9.2	242

TABLE III. MEDIAN PROTECTIVE DOSE OF SOME ANTIHISTAMINICS AGAINST INHALATORY HISTAMINE EFFECT IN THE GUINEA PIG

1	2	3	4	5	6
Drug (subcutaneously)	N*	PD_{50}		Potency	T.I.
		mgm/kgm	s.e.		
Hista-3, 15	125	0.042	0.005	102.4	910
Neoantergan	85	0.043	0.004	100**	567
Multergan	25	0.048	0.006	89.6	139
Phenergan	55	0.356	0.024	12.1	119
Neohetramine	90	0.808	0.066	5.3	47
Trimeton	72	0.895	0.087	4.8	92
Histadyl	40	1.025	0.089	4.3	14.5
Thephorin	55	1.168	0.096	3.7	21
Antistin	35	1.310	0.105	3.3	13

*Number of animals.
**Standard of reference.

ditional data, quoted from the literature,[17,16,41,6] were inserted in the table. Wherever possible, toxicity data for three species of animals were procured; as can be seen, the same drug differs usually very little in toxicity for the three species.

Antihistaminic and Anticholinergic Activities.—Data on the activity of the individual drugs of this study in the four antihistaminic tests selected are surveyed in Tables II to V. A major result of these potency assays is that all drugs subjected to the four tests appear in each of them in approximately the same sequence, although the general level of activity differs greatly in each of the four tests. This similarity in potency rank of the drugs in their various antihistaminic activities is quite at variance from their activity in the other two tests, namely, their acute toxicity (Table I) and their anticholinergic activity (surveyed in Table VI); in these two activities, the drugs rank in a quite different sequence. These differences are best visualized in Table VII where the drugs are numbered according to their ranking in the test activity dealt with in the individual column. The similarity of sequence in all four antihistaminic tests suggests that these activities are indeed due to pharmacologic mechanisms which are similarly operative in all drugs. This deserves some emphasis in view of the fact

TABLE IV. MEDIAN EFFECTIVE DOSE OF SOME ANTIHISTAMINICS, DIMINISHING BY FIFTY PERCENT THE HISTAMINE-PRODUCED SPASM OF ISOLATED GUINEA PIG GUT

1	2	3	4	5	6	7
Drug	N*	ED_{50}			Potency	T.I./10000
		Concentrat.	ug/cc.	s.e.		
Neoantergan	32	$2.3 : 10^9$	0.0023	0.0003	100.0	1065
Hista-3, 15	45	$2.8 : 10^9$	0.0028	0.0001	82.2	1359
Phenergan	25	$5.9 : 10^9$	0.0059	0.0007	39.0	720
Neohetramine	28	$1.3 : 10^8$	0.013	0.0012	17.7	292
Trimeton	30	$1.1 : 10^8$	0.011	0.0022	20.9	655
Histadyl	25	$1.6 : 10^8$	0.013	0.0018	17.7	112
Thephorin	25	$1.6 : 10^8$	0.016	0.0022	14.4	153

*Number of experiments.

TABLE V. MEDIAN EFFECTIVE DOSE OF SOME ANTIHISTAMINICS, DIMINISHING BY FIFTY PERCENT THE VASOPRESSOR EFFECT OF HISTAMINE IN RABBITS

1	2	3	4	5	6
Drug (intrajugularly)	N	ED_{50}		Potency	T.I.
		mgm/kgm	s.e.		
Neoantergan	15	0.0083	0.00052	100	2940
Hista-3, 15	20	0.0038	0.00048	84.8	3865
Neohetramine	15	0.0943	0.0096	8.8	406
Trimeton	18	0.0766	0.0112	10.8	1080
Thephorin	15	0.0835	0.0074	9.9	294

TABLE VI. MEDIAN EFFECTIVE DOSE OF SOME ANTIHISTAMINICS DIMINISHING BY FIFTY PERCENT THE ACETYLCHOLINE-PRODUCED SPASM OF ISOLATED GUINEA PIG GUT

1	2	3	4	5	6	7
Drug	N	ED_{50}			Potency	T.I./10000
		Concentrat.	ug/cc	s.e.		
Phenergan	16	$1.8 : 10^8$	0.018	0.001	10330	567
Trimeton	14	$8.0 : 10^8$	0.08	0.007	2290	139
Hista-3, 15	18	$1.6 : 10^7$	0.16	0.023	1144	119
Thephorin	15	$3.6 : 10^7$	0.36	0.023	508	47
Histadyl	15	$3.6 : 10^7$	0.36	0.031	508	92
Neohetramine	16	$3.9 : 10^7$	0.38	0.048	482	14
Antistin	14	$1.1 : 10^6$	1.1	0.93	166	21
Neoantergan	22	$1.8 : 10^6$	1.83	0.21	100	13

that the dosage range in which the individual drug operates, is different for each of the four activities, that is, that each of these activities operates on a different level of selectivity; this level, however, is the same for all substances tested, as will be shown and discussed below. It is particularly noteworthy that the fourth of the here employed antihistaminic tests also shows such satisfactory parallelity with the other three. The test function employed, a blood pressure rise in the rabbit in response to an intravenous histamine dose, which is so much in contrast to the well known depressor histamine effect in cat and dog, appears to have found little attention and no use in histamine pharmacology. Indeed, it was employed in this study

TABLE VII. ANTIHISTAMINIC DRUGS LISTED ACCORDING TO THEIR POTENCY RANK* IN EACH OF THE SIX ACTIVITIES STUDIED

1	2	3	4	5	6	7
Drug	Toxicity	Antihistaminic Potencies				(e) Anti-cholinergic Potency
		(a) Antilethal	(b) Antiasthma	(c) Antispasm.	(d) Antipressor	
Hista-3, 15	3	2	1	2	2	2
Neoantergan	1	1	2	1	1	5
Multergan	0	1.1	2.1	—	—	0
Pyribenzamine	0.1	—	—	—	—	—
Phenergan	4.1	2.1	2.2	2.1	—	0.1
Benadryl	0.3	—	—	—	—	—
Neohetramine	4(=3)	3	3	3	4	4
Diatrin	2.1	—	—	—	—	—
Trimeton	5	4	4	4	3	1
Histadyl	0.2	4.1	4.1	4.1	—	3.1(=3)
Thephorin	2(=1)	5	5	5	5	3
Antistin	0.4	—	5.1	—	—	4.1

*The most potent drug in the activity concerned is designated as 1, and so on; for drugs assayed only in some, but not all of the tests, the rank in the respective sequence is marked by intermediate numerals, 0 designating a rank higher than that of the drug ranking 1, 1,1 designating a ranking between the drug ranking 1 and that ranking 2, 1,2 designating a rank between 1,1 and 2, etc.

only because of local difficulties in obtaining the customary carnivorous laboratory animals. It is true that the vasopressor effect in the rabbit lags quantitatively, and hence in terms of selectivity level of the antihistaminic, behind the vasodepressor effect in the cat, the latter requiring by several orders of magnitude less than the former of histamine and of the antagonist. If, however, this quantitative difference may have raised doubts about the aptitude of the phenomenon for testing antihistaminics, they are repudiated by the here demonstrated parallelity between antivasopressor and other antihistaminic activities.

The differences between the rank in acute toxicity and that in the antihistaminic activities are only minor for most of the drugs, and only for a few of them, particularly Thephorin and Antistin, one may question whether death should be attributed to a mechanism unrelated to that of the antihistaminic action proper. The much more general discrepancies, however, between the rankings in anticholinergic and antihistaminic activity are certainly not in support of any hypothesis that these two actions play at closely related structures or receptors.

II. Antihistaminic Combinations

Anti-asthmatic Activity.—Determination of this antihistaminic activity was employed as the test of choice for the comparative evaluation of twenty-five binary, ternary and quaternary combinations from the series of eight antihistaminics, the antiasthma activity of which is reported in Table III. The results are presented in Table VIII. Whereas in the assay of single drugs a major basis of comparative evaluation is obtained by determining potency, P, and therapeutic index, T. I. (see columns five and six of Table III), major attention in the study of combined drugs is turned to the efficiency of the combination, C. E. (Table VIII, last column), which is the indicator of the potency of the combination as com-

TABLE VIII. MEDIAN DOSE OF SOME ANTIHISTAMINIC COMBINATIONS PROTECTING AGAINST INHALATORY HISTAMINE EFFECT IN THE GUINEA PIGS

1	2	3	4	5	6	7	8	9
No.	Antihistaminic Combination				N	PD_{50}		Efficiency (C.E.)
						mg/kg	s.e.	
1	Neoantergan 50%	Trimeton 50%			20	0.068	0.004	1.20
2	Neoantergan 10%	Trimeton 90%			20	0.285	0.032	1.07
3	Neoantergan 90%	Trimeton 10%			22	0.047	0.006	1.03
4	Neoantergan 50%	Neohetramine 50%			20	0.066	0.006	1.23
5	Neoantergan 50%	Thephorin 50%			18	0.065	0.007	1.28
6	Neoantergan 50%	Histadyl 50%			19	0.070	0.009	1.17
7	Neoantergan 50%	Antistin 50%			18	0.073	0.010	1.15
8	Neoantergan 50%	Phenergan 50%			20	0.061	0.008	1.25
9	Multergan 50%	Trimeton 50%			20	0.078	0.009	1.17
10	Multergan 50%	Neohetramine 50%			20	0.074	0.005	1.23
11	Neoantergan 33%	Trimeton 33%	Neohetramine 33%		35	0.069	0.006	1.72
12	Neoantergan 50%	Trimeton 25%	Neohetramine 25%		40	0.046	0.006	1.83
13	Neoantergan 25%	Trimeton 50%	Neohetramine 25%		30	0.090	0.008	1.67
14	Neoantergan 25%	Trimeton 25%	Neohetramine 50%		38	0.088	0.009	1.71
15*	Neoantergan 40%	Trimeton 30%	Neohetramine 30%		125	0.042	0.005	2.38
16	Neoantergan 40%	Thephorin 30%	Histadyl 30%		20	0.070	0.006	1.46
17	Multergan 40%	Trimeton 30%	Neohetramine 30%		30	0.052	0.006	2.11
18	Phenergan 40%	Trimeton 30%	Neohetramine 30%		25	0.232	0.040	2.02
19	Thephorin 33%	Trimeton 33%	Neohetramine 33%		22	0.545	0.061	1.74
20	Thephorin 33%	Trimeton 33%	Histadyl 33%		24	0.525	0.049	1.95
21	Phenergan 33%	Trimeton 33%	Neohetramine 33%		20	0.367	0.051	1.62
22	Neoantergan 25%	Trimeton 25%	Neohetramine 25%	Phenergan 25%	20	0.765	0.083	1.83
23	Neoantergan 25%	Trimeton 25%	Neohetramine 25%	Thephorin 25%	22	0.936	0.123	1.61
24	Neoantergan 25%	Trimeton 25%	Neohetramine 25%	Histadyl 25%	20	0.855	0.012	1.76
25	Neoantergan 25%	Trimeton 25%	Neohetramine 25%	Multergan 25%	25	0.049	0.005	1.76

* = Hista-3, 15.

pared with the potencies of its components. According to Table VIII, the C. E. values of all combinations are >1.0, which expresses that any two, three or four of the eight drugs reported in Table III, when combined in the ratios selected, tend to exhibit supra-additive behavior under the conditions of the asthma test employed. In many cases listed in Table VIII, the C. E. value is but little over 1.0 and, accordingly, the supra-addition indicated is devoid of significance. However, in fourteen instances, the potency of the combination is more than one and one-half, and in four it is practically twice or more than twice that expected on the assumption of merely isoadditive behavior of the components. It will be noted that all the ternary and quaternary combinations are markedly supra-additive, whereas all binary combinations are practically additive. No explanation of this interesting difference is as yet possible. Nor can an explanation be expected before the still completely obscure mechanisms of co-operation between combined drugs are understood. Attempts in this direction, up to date, necessarily start with arbitrary assumptions; the here adopted, merely pragmatic, use of the term "addition" strictly dispenses with any hypothetical premises. On this basis of evaluation, the present antiasthma experiments express that in this activity (1) a combination of antihistaminics, at least when composed of three or four drugs, is equipotent to any one of the components in a combined dose, the moieties of which are considerably smaller than the sum of proportionate moieties composing the equipotent dose of the single drug, and (2) the ternary combination Hista-3,15 ranks first among the combinations studied.

TABLE IX. EVALUATION OF THE EFFICIENCY OF THE ANTIHISTAMINIC COMBINATION, HISTA-3, 15

1	2	3	4	5	6
	D_{50}		p*	Efficiency in Reference to:	
	Found	Calculated		Potency	T.I.
Acute toxicity (Table I)	36.0	35.5	—	0.93	—
Experimental Asthma (Table III)	0.042	0.100	<0.01	2.38	2.56
Protection against death from i.-v. histamine (Table II)	0.016	0.020	<0.05	1.29	1.38
Inhibition of vasopressor effect of histamine on rabbits (Table V)	0.009	0.018	<0.01	2.05	1.93
Inhibition of histamine spasm of isolated ileum (Table IV.)	0.002	0.005	<0.05	1.99	1.71
Inhibition of acet.-choline spasm of isolated ileum (Table VI)	0.166	0.212	<0.01	1.28	0.83

*Probability value of the statistical significance of the difference between the values in columns 2 and 3.

III. Analysis of the Actions of the Ternary Combination, Hista-3,15

Spectrum of Actions of Ternary Antihistaminic Combination (Hista- 3, 15).—Because of its uppermost ranking in the asthma test, Hista-3,15 was selected for a more detailed study. It was subjected to all the five other tests which, as reported in section I, were performed with individual antihistaminics. The results of these assays of Hista-3,15 are entered, side to side with those of the individual drugs, in the respective Tables I to VI, and the combination is inserted, according to its rank in all six tests, in the respective columns of Table VII. Moreover, the potency data ascertained for the combination are assembled in Table IX (column 5), in which, in addition, also the combinatory efficiency, C. E., with regard to each of the four antihistaminic activities and the anticholinergic activity is recorded in column 6. As is best visible in Table VII, Hista-3,15 vies in all antihistaminic tests with the most potent one of its components, Neoantergan, for the first rank in potency. In acute toxicity, however, while on equal level with Neohetramine, its one component, it ranks not only behind the second, Neoantergan, but also behind the majority of the numerous other antihistaminics tested, and only its third component, Trimeton, lags in toxicity behind it (see Tables I and VII). In anticholinergic potency, in turn, it holds again second rank behind Trimeton and is superior to its other two components. Still more significant for the differences in action spectrum between the combination and its components are the values of combinatory efficiency, C. E. In all antihistaminic activities, least of them in antilethal activity, and also in anticholinergic activity, the combination's C. E. is significantly >1.0 and in three instances of antihistaminic activity even near or above 2.0, that is, in these activities the combination is supra-additive, whereas for its toxicity (C. E.=0.93) there is rather an indication of infra-additive behavior. The meaning and the basis of all these characteristics of the combination will be better understood after an evaluation of the selectivity features of the combination and its components (see below).

TABLE X. VARIATION OF THE LETHAL DOSE OF HISTAMINE WITH THE DOSE OF HISTA-3, 15 GIVEN FOR PROTECTION

1	2	3	4	5	6	7
	Animals dead/used	Drugs (intrajugularly)		LD_{50}		
		Histamine mgm/kgm	Hista-3, 15 μgm/kgm	mgm/kgm	s.e.	$LD_{50}/0.6$
I	2/10 2/5 6/10 5/7	0.3 0.4 0.7 0.9	0 0 0 0	0.6	0.07	1
II	1/6 2/6 4/6	2 4 8	10 10 10	5.6	0.7	9.3
III	1/6 2/3 4/5	10 20 30	30 30 30	16.5	3.5	27.5
IV	1/5 3/5 3/4	30 40 50	100 100 100	46.0	5.5	76.7
V	1/5 3/5 4/5	50 80 100	200 200 200	73.0	9.1	121.5

Variation of the Lethal Dose of Histamine with the Dose of Antihistaminic Combination.—In regard to one of the four antihistaminic activities of the Hista-3,15 combination, namely, its antilethal activity (a), the above reported studies were extended to include determinations of several PD_{50} of the combination at more than the one, usually here investigated endpoint. This was done in order to obtain information on the nature of the functional relationship between the amounts of histamine detoxified and those of the protective drug administered before the injection of the supralethal histamine amounts. Hista-3,15 was selected as the antihistamine for these experiments because it appeared of interest to learn about the nature of this relationship when the protection is exerted by a combination of antihistaminics. For single antihistaminics, the problem has been studied in two instances—Benadryl[39] and Thephorin[17]—and in both cases a linear relationship between the amounts of agonist and antagonist was disclosed. The results of the present study, as accounted for in Table X and illustrated in Figure 1, demonstrate that the relationship is of the same linear type. The conclusion is suggested that, insofar as the nature of the relationship studied allows conclusions about the mechanism of action, the mechanism of the histamine antagonism exerted by a combination of antihistaminics is the same as that exerted by a single antihistaminic.

Relationship between Antihistaminic and Anticholinergic Activities.—That the relation between these two types of activity is different for each antihistaminic, is disclosed by the experiments reported and has been discussed in a preceding section. To visualize this inconsistency, and to illustrate the position of the combination in reference to its components and to

some other individual drugs, the experimental data on the antispasmodic activities c and e, namely, versus histamine and acetylcholine spasms of the isolated guinea pig ileum, were condensed into a nomogram elaborated according to Schild's procedure.[31] As in Schild's studies, the nomogram (Fig. 2) juxtaposes the logarithms of the molar concentrations of each antihista-

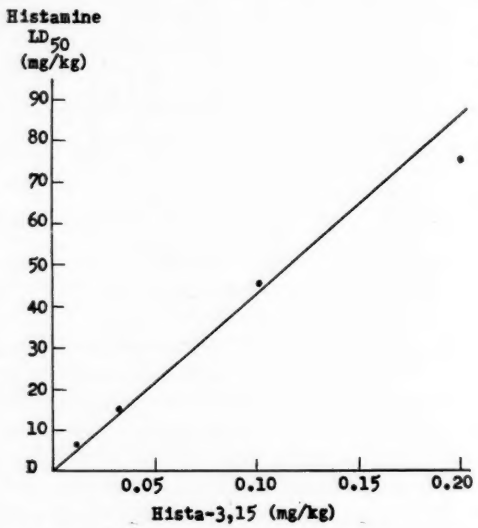

Fig. 1. Relationship between progressive doses of Hista-3,15 and lethal doses of histamine.

minic, which reduced by 50 per cent the spasmodic effect of histamine (pAc) and of acetylcholine (pAe), respectively, and connects the two values of each drug by a line, the slope of which visualizes the degree of preference given by the drug to antihistaminic over anticholinergic activity, or, in the terms to be employed in the subsequent section, the degree of antihistaminic selectivity of the drug in reference to its anticholinergic activity. The pA values on the basis of our own experiments are quite similar to those obtained by Schild,[31] Velásquez and García[38] and Reuse.[30] The graph shows that the combination is intermediate in the antihistaminic selectivity studied between that of its maximally selective component, Neoantergan, and that of its other two components, and is considerably more selective than the drug of least selectivity, Phenergan.

Evaluation of Selectivity Characteristics of three Antihistaminic Drugs and their Combination.—Such evaluation, according to the principles described under "Methods," was performed for Neoantergan, Neohetramine and Trimeton, and for their combination in the ratio of 4:3:3, Hista-3,15,

with regard to their four antihistaminic activities tested (a to d) and their anticholinergic activity (e). Table XI surveys in its first part the doses which were taken as the basis of the evaluation, namely those equieffective in antagonizing 1.0 mg of histamine and acetylcholine, respectively, and in its second part the potencies calculated therefrom in reference to the anti-

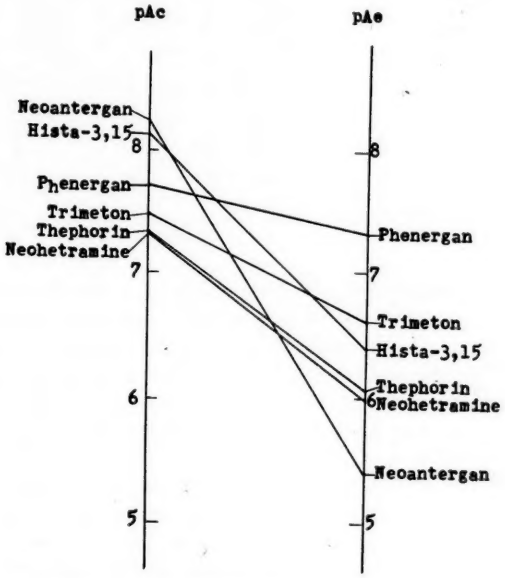

Fig. 2. Antihistaminic and anticholinergic activity of some antihistaminics on isolated guinea pig ileum. (For symbols see text.)

spasmodic potency of Neohetramine. Table XII presents the results of employing these potency values for calculating the degree of relative selectivity, D. S. As explained in the section on methods, the D. S. values in columns 2 to 9 of the table indicate how many times greater the activity named in the numerator of the potency ratio at the head of the column is than that in the denominator. Thus, the table gives, along each horizontal line, an estimate of the dosage range in which each activity of the same drug operates selectively, that is, without interference by the other activity named in the ratio concerned; vertically, within each column, the table indicates how much the range of the same type of selectivity differs between the drugs considered. For instance, the table expresses that for Neoantergan 807 times the dose spasmolytic for histamine spasm in the guinea pig ileum is required to induce an equivalent lysis of acetylcholine-produced spasm, whereas only a 7.3-fold increase in dose is required in the case of Trimeton. The table also indicates that for all four drugs activity

TABLE XI. EQUIEFFECTIVENESS AND POTENCY VALUES FOR THE ANTIHISTAMINIC AND ANTICHOLINERGIC ACTIVITIES OF THREE ANTIHISTAMINICS* AND THEIR TERNARY COMBINATION**

Activity	N-A	N-H	Tr	H-3
	A. Equieffective Doses			
a. Anti-lethal (μg/kg)	0.94	6.78	9.7	1.55
b. Anti-asthma (μg/kg)	17.2	324.0	358.0	16.4
c. Anti-spasmodic (μg/kg)	230.0	1300.0	1100.0	280.0
d. Anti-vasopressor (μg/kg)	41.5	474.0	383.0	49.0
e. Anticholinergic (μg/kg)	183000.00	38000.0	8000.0	16000.0
	B. Potencies (referred to Pe of N-H)			
a. Anti-lethal	1382.00	192.00	134.00	840.00
b. Anti-asthma	67.00	4.00	3.63	82.50
c. Anti-spasmodic	5.65	1.00	1.18	4.65
d. Anti-vasopressor	31.70	2.74	3.40	26.60
e. Anticholinergic	0.007	0.034	0.162	0.08

* N-A = Neoantergan, N-H = Neohetramine, Tr = Trimeton.
** H-3 = Hista-3, 15.

a is the one of highest selectivity, that activity *b* is for all four drugs next in selectivity ("second order of selectivity"[19]) and that, again for all four drugs alike, levels of selectivity progress in the sequence a>b>d>c>e. Notwithstanding this uniformity of the levels on which the various activities are found, the width of the range, in which each of them plays, varies greatly from one drug to the other. This variation is expressed by the ratios of comparative selectivity, S. R., which are surveyed in Table XIII. The many instructive differences disclosed by this evaluation cannot be discussed in all detail within the limited frame of this paper, but are evident from the tables, especially Table XIII. The following major differences between the combination and its components may be pointed out here: The position of Hista-3,15 in reference to its three components varies with the activity considered. For instance, it is inferior in S. R. to all its components in activity a, the antagonism to that part of the histamine action spectrum which is responsible for lethal effect of intravenously given histamine (Table XIII, line 1), a histamine activity the pathogenic significance of which is rather obscure. That signifies that the next-selective antihistamine action (b), whose therapeutic significance is certainly less doubtful, is correspondingly more accentuated in the combination. In this activity, the combination has a higher S. R. than any of its components (b/d, line 6) and the same holds true for its selectivity in activity d (d/c, line 8). In anticholinergic activity, whether expressed by the ratio of a, b, c or d over e (lines 4, 7, and 9, respectively), the combination holds an intermediate position; it shows neither the extreme antihistaminic selectivity of Neoantergan nor the comparatively narrow span between antihistaminic and anticholinergic activity characteristic of Trimeton and Neohetramin.

In addition to these selectivity differences between components and combination, the nature of the synergism between the components is also important for the over-all evaluation of the combined drug, namely, the con-

TABLE XII. POTENCY RATIOS
(Degree of relative selectivity, D. S.)

1	2	3	4	5	6	7	8	9
Activity type	a/b	a/d	a/c	a/e	b/d	b/c	d/c	c/e
Activity level	I	I+II	I to III	I to IV	II	II+III	III	IV
Neoantergan	20.6	44.6	245	197428	2.1	11.8	5.6	807.0
Neohetramine	48.0	70.0	192	5650	1.4	4.0	2.7	29.4
Trimeton	37.0	39.4	113	828	1.07	3.0	2.9	7.3
Hista-3, 15	10.2	32.3	180	105000	3.1	17.7	5.7	58.1

TABLE XIII. COMPARATIVE SELECTIVITY RATIOS (S.R.) OF THE FOUR DRUGS ON VARIOUS SELECTIVITY LEVELS

1	2	3	4	5	6
Curr. Nr.	Activity	Level	Activity Range Covered	Drugs (in sequence of their S.R.)	S.R. (comparative selectivity)
1	a	I	a/b	N-H>Tr>N-A>H-3	4.7: 3.6: 2.0: 1
2	a	I to III	a/c	N-A>NH>H-3>Tr	2.2: 1.7: 1.6: 1
3	a	I+II	a/d	N-H>N->ATr>H-3	2.2: 1.4: 1.2: 1
4	a	I to IV	a/e	N-A>H-3>N-H>Tr	238.0: 127: 6.8: 1
5	b	II+III	b/c	H-3>N-A>N-H>Tr	5.9: 3.9: 1.3: 1
6	b	II	b/d	H-3>N-A>N-H>Tr	2.9: 1.9: 1.3: 1
7	b	II to IV	b/e	N-A>H-3>N-H>Tr	442.0: 46 : 5.3: 1
8	d	III	d/c	H-3>N-A>Tr>N-H	2.1: 2.1: 1.1: 1
9	c	IV	c/e	N-A>H-3>N-H>Tr	110.0: 8.0: 4.0: 1

N-H = Neoantergan, N-H = Neohetramine, Tr = Trimeton, H-3 = Hista-3, 15

comitance of (1) a supra-additive synergism in regard to their antihistaminic activities, most outstanding in the antiasthma activity, (2) their merely additively combined toxicity and (3) their little supra-additive cooperation in anticholinergic activity.

In regard to antiasthma activity, the advantages of Hista-3,15 were found, although to a lesser degree, also in the other ternary and quaternary combinations studied. It would be interesting whether the additional peculiarities disclosed by the more detailed study of this one combination are also shared by those other combinations. It may be considered of still greater interest how the experimentally established characteristics of the ternary combination will be reflected when Hista-3,15 will be compared in therapeutic use with its clinically well established components. The mutual potentiation of the components, limited to the major antihistaminic activities—a phenomenon which explains the desirably large therapeutic index—is certainly promising, and those who attribute significance to other than merely histaminic pathogenic factors in allergic disorders may see another advantage in the equilibration between antihistaminic and anticholinergic action.

SUMMARY

1. Acute toxicity in three species of animals and antagonism against four different actions of histamine—lethal action at intravenous administration to the guinea pig, inhalatory "asthma" in the guinea pig, vasopres-

sor action in the rabbit, and spastic action upon the isolated guinea pig ileum—as well as against acetylcholine spasms of isolated guinea pig gut were measured for a series of customary antihistaminics, and potency and therapeutic index were determined in each instance.

2. Measurement of antihistaminic activity in the "asthma" test was then employed for a comparative study of ten binary, eleven ternary and four quaternary combinations of eight of those singly studied drugs, namely, Antistin, Histadyl, Multergan, Neoantergan, Neohetramine, Phenergan, Thephorin and Trimeton, and evaluated by determining, in addition to the potency of the combinations, their "efficiency," that is, a value expressing whether, and to what degree, the combinations deviate from their components either supra- or infra-additively.

3. All the binary combinations exhibited only an insignificant, all ternary and quaternary combinations, however, a significant supra-additive effect ("potentiation"); the highest degree of potentiation, almost two and one-half times the additively calculated effect, was found embodied in a combination of Neoantergan, Neohetramine and Trimeton ("Hista-3,15").

4. On the basis of this finding, all parts of the action spectrum of this ternary combination were studied in analogy to those studied in the single drugs, and the data obtained were employed for a detailed comparative evaluation of the action spectrum and the degree and type of selectivity of the various actions of the combination and its components. According to this evaluation, the combination is characterized by (a) supra-additive synergism in counteracting experimental histamine asthma and, to a somewhat lesser degree, other histamine actions, (b) lack of supra-additive toxicity and (c) merely additive anticholinergic activity, furthermore (d) a greater selectivity ratio than the components in its action against histamine asthma and some of its other antihistaminic actions, and (e) an intermediate position between the extreme antihistaminic selectivity of Neoantergan and the much narrower margin between antihistaminic and anticholinergic activity of Neohetramine and Trimeton.

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MEASUREMENT OF GASTRIC ACIDITY FOLLOWING ORAL ADMINISTRATION OF THEOPHYLLINE

SAMUEL H. WAXLER, Ph.D., M.D.
San Francisco, California

IT IS generally maintained that the oral administration of theophylline preparations in therapeutic doses is limited by gastrointestinal disturbances. On the basis of this clinical impression, a variety of theophylline compounds have been prepared in an attempt to avoid these side-reactions. Although much is made of the low degree of tolerance to the oral use of these xanthine drugs few reports on this point are well developed.

When Krasnow and Grossman[1] reported that oral aminophylline induced a marked increase in gastric acidity, it was thought desirable to ascertain whether this hyperacidity was constant with various theophylline preparations and possibly a source of gastric discomfort. Blood theophylline levels were determined at the time that gastric samples were taken in an attempt to correlate gastric secretion with the various drugs.

MATERIALS AND METHOD

Five young adults, with no present or past history of gastrointestinal difficulty, were used in this study. On the morning of the experiment after a twelve hour fast, a Levine tube was introduced quickly into the stomach and the gastric contents aspirated. The material which was collected was analyzed for free hydrochloric acid, and total acid, and considered as the pre-treatment control. Each person was then given a 250 mgm. tablet of a theophylline preparation at 12 noon, at 6 p. m., at 12 midnight and at 6 a. m. the following morning, a total of 1 gram during this eighteen-hour period. Two hours after the last tablet had been swallowed, the experimental sample of gastric juice was withdrawn and also 10 cc of blood was taken. This experiment was repeated at three different times with the following theophylline preparations: theophylline, aminophylline and calphyllin.[3] Blood samples were analyzed for their theophylline content by the ultraviolet spectrophotometric methods in a Beckman DU spectrophotometer.[2] The gastric juices were determined for acidity by the usual Topfer method.

RESULTS

The results, obtained on five patients taking the three different theophylline compounds, are represented in Figure 1. There is no apparent difference in the gastric analyses in any of the patients as the result of the administration of oral theophylline. The pre-treatment gastric juices aver-

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This study was supported by a grant from G. D. Searle & Co.

GASTRIC ANALYSES									BLOOD THEOPHYLLINE LEVELS		
PATIENTS	BLANK		THEOPHYLLINE		AMINOPHYLLINE		CALPHYLLIN		THEOPHYL-LINE	AMINOPHYL-LINE	CALPHYL-LIN
	Free HCL	Total Acid	Free HCL	Total Acid	Free HCL	Total Acid	Free HCL	Total Acid			
B	6	29	0	14	2	25	4	26	1296	898	793
F	13	42	18	40	20	50	18	50	681	641	664
M	0	12	8	36	2	20	10	50	1141	1261	1096
C	8	31	2	28	0	20	0	8	1118	900	1026
H	26	55	15	47	10	54	10	40	930	949	718
AVERAGE	11	34	9	31	7	34	9	35	1033	930	860
	(DEGREES)								MICROGRAMS PER 100 cc OF BLOOD		

Fig. 1. Gastric analyses before and after oral administration of theophylline preparations. Blood theophylline levels at time of gastric analyses.

aged 11° for free hydrochloric and 34° for total acid. The results for theophylline were 9° and 31°; for aminophylline 7° and 34° and for calphyllin 9° and 35°. The blood theophylline levels averaged 1033, 930 and 860 mcg per 100 ml of blood respectively. None of the five subjects noted any gastric distress or consciousness during or immediately after the test.

DISCUSSION

It was reported by Krasnow and Grossman that aminophylline produces a marked stimulation of the secretion of gastric juice in man on oral or intravenous administration. Their method of procedure for oral administration consisted of giving 0.5 gm of aminophylline in 300 cc of water by Levine tube. The tube was left in place during the two hours of experiment and samples drawn at intervals. Although they demonstrated a definite rise in acidity with this technique, they noted, however, that three patients given aminophylline in the tablet form had variable response but no data were given. Our patients were given 1 gm of any of the three theophylline compounds during an eighteen hour period and showed no apparent stimulation of gastric secretion. The blood theophylline levels were of a high order and show definite theophylline absorption and retention during this time. Thus we must assume that the technique of administration may have accounted in some degree for the stimulation which has been reported. It appears that under the usual administration of oral uncoated theophylline tablets there is no increase in the acidity of the stomach.

SUMMARY

There was no demonstrable stimulation of gastric secretion in patients following oral administration of theophylline preparations in tablet form.

There is no increase in the free hydrochloric acid or total acidity even when theophylline determinations indicate definite absorption with high blood levels of theophylline.

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AMERICAN ACADEMY OF ALLERGY

Dr. Ben Z. Rappaport, president of the American Academy of Allergy, has announced the annual meeting of the Academy to be held at the Shamrock Hotel, Houston, Texas, February 1-3, 1954. This will be preceded by the Annual Postgraduate Course, January 29, 30, 31, 1954. These courses are open to physicians, technicians and those engaged in allergy research. All sessions of the Postgraduate Course will be held at the Baylor University College of Medicine.

The guest speaker for Monday, February 1, will be Dr. William Dameshek, who will speak on "The Development of Immuno-hematologic Concepts." On Tuesday, February 2, the guest speaker will be Dr. Frank S. Dixon, who will speak on "The Dynamics of the Immune Response."

Make your hotel reservations now, by writing directly to the Shamrock Hotel, Houston, Texas. Reservations for the Postgraduate Course should be made through Mr. A. H. Luthmers, 208 East Wisconsin Avenue, Milwaukee, Wisconsin.

STANDARDIZATION AND ANTIGENIC ANALYSIS OF POLLEN EXTRACTS BY GEL DIFFUSION

(An Abridgement)

R. P. WODEHOUSE, Ph.D.
Pearl River, New York

IN ANTIGENIC analysis by gel diffusion, antigens are caused to react with their homologous precipitating antibodies in a semisolid medium such as gelatin or agar. Generally, the antiserum is combined with the gelatinous phase and the antigen put in the liquid phase supernatant upon it. For quantitative tests this is done in flocculation tubes kept at refrigeration temperature.

As the antigen diffuses into the homogenous antibody layer and its concentration becomes equivalent with that of the antibody, a precipitating band is formed. As more antigen enters the antibody phase, the equivalence zone progresses steadily away from the interphase boundary indicated by the moving precipitation band. This band usually presents a sharp leading edge but a very poorly defined trailing zone which is in the region of developing antigen excess in which the precipitate is always more or less soluble (Fig. 1A). It is more soluble with horse antiserum and less with that of rabbit. Consequently, with horse antisera, the precipitating bands are narrow (Fig. 2), whereas with rabbit antisera they are broad and nebulous in the trailing zone, causing much overlapping when there are more than one.

The dynamics of such precipitating systems are those of ordinary diffusion. The precipitate, as formed and redissolved, is merely a convenient marker whereby we may watch the progress of the diffusing antigens. Consequently, the laws of diffusion may be applied here with the same degree of accuracy as in purely physical systems.

The laws of diffusion state that its rate is proportional to the square root of the time, and some fractional power of the concentration of the diffusing substance. Hence, the distance traversed by a precipitating band at any given time, or its rate of penetration, is a measure of the concentration of the antigen. Or, if the rate of penetration (P) is plotted on co-ordinate paper against the logarithm of the concentration, the points will fall in a straight line. This is most easily done by using semilogarithmic co-ordinate paper and recording the actual antigenic concentrations in the logarithmic scale.

This method of assaying antigens is known as the Oudin technique because Jacques Oudin of the Pasteure Institute, Paris, was the first to demonstrate that the physical laws of diffusion could be applied to immunological precipitating systems in semisolid media.

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Dr. Wodehouse is an Associate Fellow of the American College of Allergists.

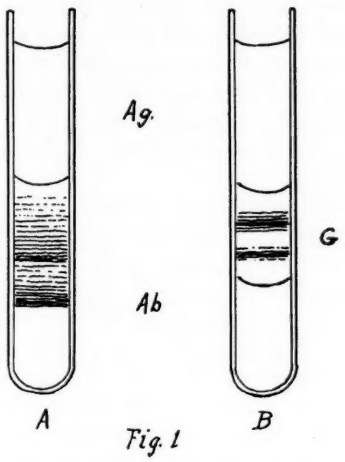

Fig. 1

Fig. 1. Serum-agar diffusion with rabbit antiserum. A. Single diffusion. B. Double diffusion. Ag. Antigenic extract. Ab. Antiserum in agar. G. Plain agar.

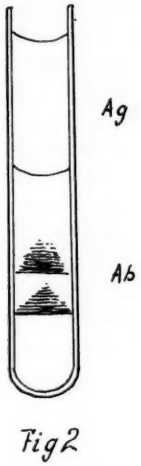

Fig 2

Fig. 2. Single diffusion with horse antiserum in agar. Symbols as in Figure 1.

Oudin discovered that when he let crude antigenic substances, such as horse serum, egg white or toxoids diffuse into their homolgous antisera, many precipitating bands were always formed; only with highly purified substances did a single band appear. And if he combined two or more such systems, he got correspondingly as many precipitating bands. Consequently, each band represents at least one antigen-antibody reaction, sometimes more because it quite often happens that two or more bands move at so nearly the same rate that they become superimposed.

The fact that most precipitating bands move at different rates gives a means of antigenic analysis. However, with the Oudin technique, particularly if rabbit antisera are used, the bands are not easily distinguished because of their tendency to overlap. Thus the Oudin technique, while ideal for quantitative measurements, does not lend itself to qualitative analysis.

A much better method has been devised by Örjan Ouchterlony called the method of double diffusion. The antigens and antisera are allowed to diffuse through neutral agar in such a way that they meet and form precipitating bands between their sources. There are a number of ways of accomplishing this. The simplest is to interpose in the Oudin tubes a layer of neutral agar between the antibody and antigen phases (Fig. 1B). After several days the antigens diffusing downward will meet the antibodies diffusing upward and form precipitating bands. At first these

may be faint and move in the direction of the weaker component, but as zones of equivalence are established the bands tend to become stabilized at varying distances from the sources of their components, depending upon the relative mobilities of these. Further diffusion of antigen and antibody into the sites results only in an intensification of the bands. Moreover, such bands are narrow, sharp on both edges, and in time develop great intensity and disparateness.

A better use of the double diffusion principle in antigenic analysis is the "punch plate" method of Ouchterlony. A thin layer of neutral agar is poured into a petri dish and allowed to set. Then metal templets are placed on it in any desired arrangement, and a second layer of neutral agar poured in. When this has hardened the templets are removed leaving little wells into which are poured the reactants to be examined. A simpler way, and one which gives excellent results, is to substitute penicillin cups for the little wells, as in the "cup plate" assay of antibiotics. These cups are metal or glass cylinders about 10 mm long and 7.5 mm in diameter, open at both ends. When stood on the surface of the agar they may be filled with the reactants, which then diffuse from them into the agar. Generally three such wells or cups are used equally spaced from each other. In two are placed the two antigens to be compared and in the third is placed the antiserum of one or the other or a combination of the two.

Ouchterlony has shown that with such an arrangement: (1) if the antigens are identical their precipitating bands, interfere with each other and form symmetrical arches over the serum well (Fig. 3); if the antigens are the same in kind but different in amounts, the arch will be distorted toward the well containing the weaker antigen (Fig. 4); (3) if an antigen in one is insufficiently concentrated to produce a precipitate of its own it may still be able to bend the approaching end of the precipitating band from the other making it unsymmetrical (Fig. 5); (4) antigens which are different will produce precipitating bands which cross without interference, providing their two antisera are combined in the serum well (Fig. 6).

Bertyl Björklund has shown that by pretreating the diffusion medium with one or more of the antigens in a complex system the precipitating bands for these may be completely inhibited without interfering with the others. This may be done by mixing the inhibiting antigens with the diffusion medium by putting them in all three wells and allowing them to diffuse into the medium before the reactants are added, or by combining them with the antiserum in optimal proportions. For example, if one is studying the antigenic make-up of various organs such as kidney, liver or spleen, the organ antigens are unavoidably contaminated with blood. In fact more precipitating bands are likely to come from the plasma antigens and antibodies than from those of the organs themselves. However, Björklund showed that such can be specifically inhibited by pretreating

the diffusion medium with plasma. The bands remaining will then be due only to the tissues under investigation (Figs. 7 and 8).

These principles, with certain modifications, can be applied to all allergenic extracts.

In these studies, rabbit antisera were used. They are prepared by injecting the pollen extracts combined with Freund's adjuvant at multiple

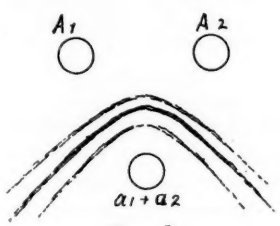

Fig. 3

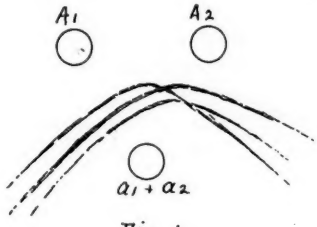

Fig. 4

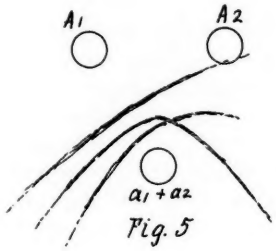

Fig. 5

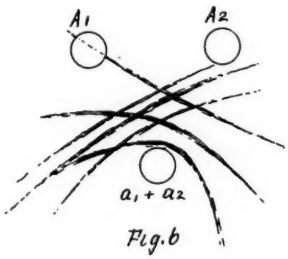

Fig. 6

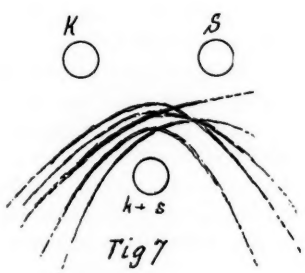

Fig 7

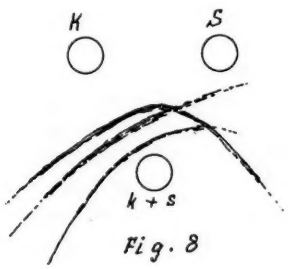

Fig. 8

Figs. 3 to 8. Antigenic extracts compared by cup-plate method. A_1, A_2—Antigenic extracts, a_1, a_2 their homologous antisera.

Fig. 3. Antigenic extracts identical.

Fig. 4. Antigens common to both extracts but the first two weaker in extract A_2.

Fig. 5. Antigen No. 1 much weaker in A_2, No. 3 absent, but No. 2 equal in both.

Fig. 6. All antigens different in extracts A and B.

Figs. 7, 8.—K, kidney; S, spleen extract, k, kidney antiserum; s, spleen antiserum. Fig. 7 uninhibited, Fig. 8 inhibited with plasma (simplified for purpose of display).

TABLE I. DILUTIONS OF ANTIGENS COMPARED

Pollen Units p. ml.	66 hrs.				90 hrs.				114 hrs.				P Averages	
	S		U		S		U		S		U			
	D	P	D	P	D	P	D	P	D	P	D	P	S	U
6.5	4.1	.505	2.9	.357	4.8	.480	3.35	.353	5.3	.497	3.57	.351	.494	.354
9.0	4.6	.567	3.7	.456	5.5	.580	4.0	.422	6.3	.591	4.6	.431	.579	.436
12	5.2	.641	4.0	.493	6.1	.643	4.6	.485	6.8	.638	5.25	.492	.641	.490
15	5.7	.702	4.4	.542	6.6	.697	5.1	.538	7.35	.689	5.75	.539	.696	.539
20	6.15	.758	4.9	.603	7.4	.780	5.75	.607	8.0	.750	6.5	.609	.763	.606

S, standard ragweed extract. U, the 'unknown,' actually a 2-fold dilution of S. D, distance of penetration. P, penetration rate $P = \frac{D}{\sqrt{T}}$

sites. About 2.5 million units are given in 10 ml as the first injection and one half this amount at weekly intervals thereafter for six weeks. Two weeks later the animals are bled from the heart and the serum recovered in the usual way. Antisera of the same kind are pooled, merthiolate 1:5000 added, shell frozen, and are stored in a freezer.

For use, the serum is combined with 0.6 per cent agar in equal parts, also containing 1:5000 merthiolate. Of this 0.75 ml is pipetted into flocculation tubes and allowed to set in the refrigerator. Then the extracts to be tested are poured on in duplicate or triplicate tubes, and returned to the refrigerator for twenty-four or forty-eight hours. They are then examined by means of a slit lamp, with oblique lighting against a black background. This causes the bands to stand out like luminous clouds in a dark sky. The progress of the advancing bands is measured by a vernier caliper held against the outside of the tube. The duplicate or triplicate measurements are averaged unless more than 0.3 mm apart, which seldom happens.

With pollen extracts there are always more bands than one. With short ragweed seven can be distinguished, though seldom all at once. The fastest moving, designated as the *a* band, is nebulous and without sharp boundaries, rendering it unfit for measuring. The next or *b* band, though much slower, is the most distinct of all and easily recognized. It appears to account for more of the precipitate than all the others together. So it is the one chosen for quantitative work. In the Oudin tubes, generally one or more other bands can be seen at the same time, but these move slower and overlap to a degree that makes them unserviceable.

The applicability o principles of diffusion to assaying pollen extracts was put to the test as follows: From a standard short ragweed extract was made a dilution of 1:2 by adding an equal volume of saline. From the undiluted standard were made five dilutions (S Table I). The diluted fraction was treated as unknown and diluted in exactly the same way (U Table I). These two series of dilutions were then poured over antishort-ragweed serum-agar. The distance of penetration of the *b* band was measured at three different time intervals (D Table 1). It is seen

that the distance of penetration is considerably greater for the standard than for the "unknown" extract at any given time. If these distances are plotted against the square root of the time, their graphs will form straight lines, and the higher the concentration the steeper the slope,

TABLE II. ANTIGEN DILUTIONS COMPARED

Concentrations for corresponding values of P for S and U, and their ratios.

S	U	$\frac{S}{U}$
6.5	12.0	.541
7.8	15.0	.520
9.0	18.0	.500
10.0	20.0	.500
	Average	.515

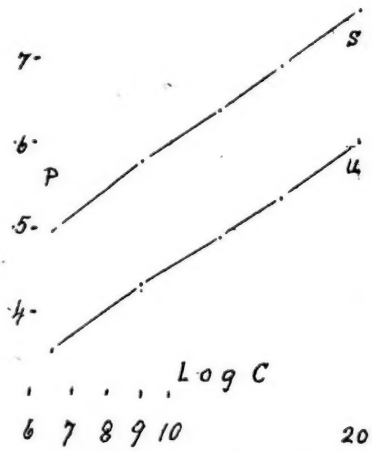

Fig. 9. Diluted and undiluted *antigens* compared average values of P for the standard (S) and for the 'unknown' (U), actually a 2-fold dilution of standard, plotted against log concentration.

with the graph of the "unknown" always less steep than that of the corresponding dilution of the standard. The rates of penetration (P) were calculated from the formula

$$P = \frac{D}{\sqrt{T}}$$

when D = the distance traversed and T = the time

It is seen that these values do not increase with the time, but do increase with the concentration, and those of the standard are always above those of the "unknown." The values are shown plotted against the logarithm of their concentration in Figure 9. From these two graphs corresponding values of P can be read in terms of units per ml. These are shown in Table II together with the ratios of standard to "unknown." The average is .515 which tells us that the "unknown" is 51.5 per cent of the standard in antigenic activity. We already know that it was made from material which was exactly 50 per cent of the standard. Thus it is seen that one pollen extract can be assayed in terms of another with a reasonable degree of accuracy.

TABLE III. SERUM DILUTIONS COMPARED

Serum Dilutions	24.5 hrs.				48.5 hrs.				119.5 hrs.			
	S		U		S		U		S		U	
	D	P	D	P	D	P	D	P	D	P	D	P
1:1	3.53	.713	4.4	.890	4.83	.695	6.2	.892	7.23	.662	9.1	.832
1:1.5	—	—	5.03	1.015	—	—	7.07	1.015	—	—	10.1	.925
1:2	4.5	.910	5.47	1.105	6.23	.895	7.47	1.072	9.0	.823	10.9	.998
1:3	4.97	1.005	5.87	1.185	6.8	.977	8.04	1.160	10.17	.932	11.63	1.065
1:4	5.13	1.035			7.4	1.062			10.87	.994		
1:6	6.03	1.218			8.33	1.195			11.97	1.095		

S, standard anti-ragweed rabbit serum. U, the 'unknown', actually a 2-fold dilution of S.

TABLE IV. SERUM DILUTIONS COMPARED

Dilutions of corresponding values of penetration rates of S and U. From Figure 5.

24.5 hrs.			48.5 hrs.			119.5 hrs.		
S	U	S/U	S	U	S/U	S	U	S/U
1.85	1.0	1.85	1.95	1.0	1.95	2.1	1.0	2.10
2.00	1.05	1.90	2.0	1.005	1.99	2.0	.96	2.08
3.00	1.45	2.03	3.0	1.35	2.21	2.9	1.50	1.93
3.3	1.50	2.20	3.4	1.5	2.26	3.0	1.505	1.99
4.0	1.60	2.50	4.0	1.9	2.10	4.0	2.0	2.0
4.8	2.0	2.40	4.1	2.0	2.05	4.0	2.0	2.0
5.8	3.0	1.87	5.3	3.0	1.77	5.3	3.0	1.77
Average		2.11			2.05			1.99

Exactly the same procedure can be applied to assay a serum against a standard serum, only in reverse, because the weaker the serum, the faster it is penetrated by the antigen. An antiragweed serum was chosen which was known to give satisfactory precipitates in dilution of 1:6. A dilution of 1:2 was made. As before, the undiluted was treated as the standard (S) and the diluted as the "unknown" (U). Series of dilutions were made from each and combined with agar. These were overlaid with a constant concentration of ragweed extract. The penetration rates were plotted against log dilution. In this case the penetration rates of the "unknown" serum were always greater than of the standard. When the corresponding values of these are averaged it is seen that the "unknown" is 2.04 times the standard (Tables III, IV, Fig. 10). However, as before the "unknown" was purposely made twice as dilute. It is thus seen that an antiserum can be accurately assayed against a standard serum. Hence we have a choice of standards, the pollen extract or its antiserum. For a permanent national or international standard, the antiserum has the advantage because of its proved stability when kept frozen or vacuum dried from the frozen state. This has not proved to be the case with pollen extracts.

The precipitating antibody is considered thermostable, whereas the pollen antigen is thermolabile. An antiragweed rabbit serum of moderately high titre was heated at 56° C. for thirty minutes. When this was compared with an unheated portion as above the penetration rates for rag-

weed were found to average for the heated fraction 1.071 and for the unheated 1.032, a difference which, though in favor of the unheated, is within the limits of experimental error, so may or may not be significant.

Since pollen extracts are known to contain more than one antigen, any

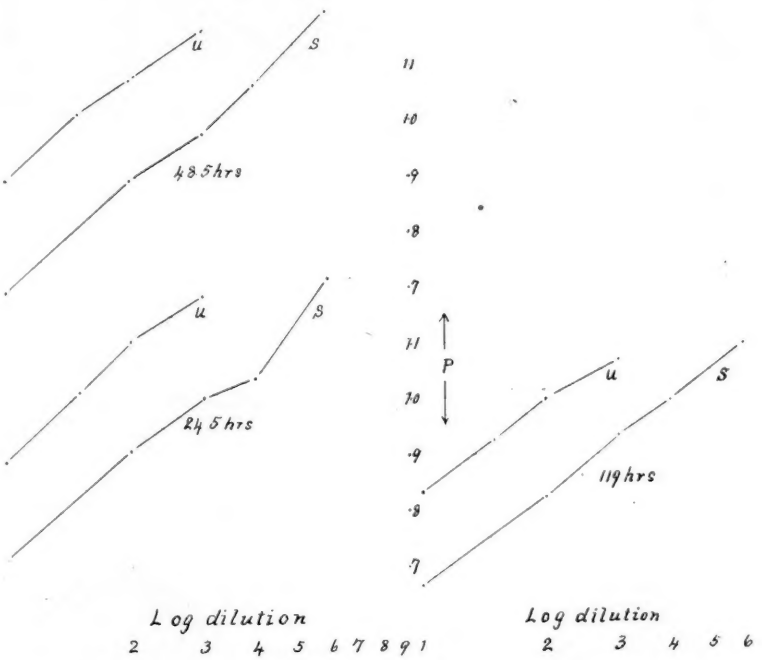

Fig. 10. Diluted and undiluted *Antisera* compared values of penetration rates (P) plotted against log dilution. S, standard; U, "unknown," actually a 2-fold dilution of standard.

method of their standardization is open to question unless all antigens are accounted for. In fact it has been argued editorially in the *Journal of Allergy* (23 (6):558, 1952) that "On theoretical grounds it appears unlikely that any simple biologic standardization would adequately solve the problem presented by a mixture of proteins, to some of which one patient is sensitive while another reacts to others."

There is no need to speculate on this problem since we can demonstrate the loss of activity of a deteriorated pollen extract by the Oudin technique, and at the same time, analyze its antigenic structure by the Ouchterlony technique.

Experiments have shown that temperature is a potent factor in the deterioration of pollen extracts. Ragweed extracts, without the protection

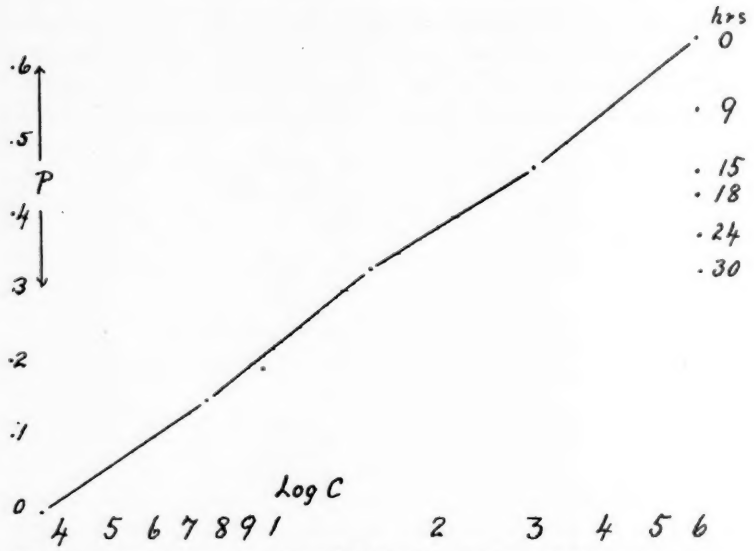

Fig. 11. Quantitative effect of artificially aging Ragweed Pollen extract. Penetration rates (P) plotted against concentrations from 3.75 to 60 thousand units per ml compared with the latter concentration heated 9, 15, 18, 24 and 30 hours at 37°C.

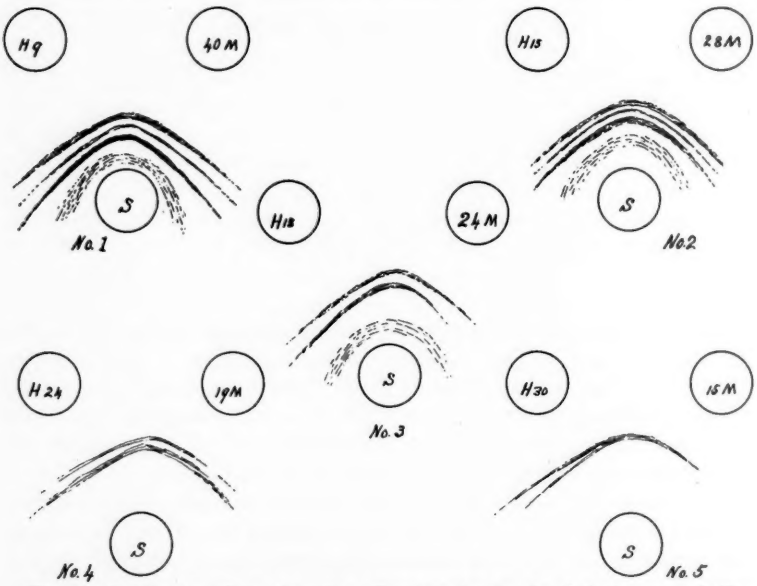

Fig. 12. Qualitative effect of heating. Precipitation bands of short ragweed dilutions compared with their heated equivalents as found from the graph, Fig. 11. H=heated 37°C for the number of hours indicated. M=1000 units per ml. The heated fractions were all 60,000-unit material.

TABLE V. STANDARDIZATION

Penetration of an unknown ragweed extract (U) compared with that of a standard extract (S).

Hours	9500 u/ml				19,000 u/ml				38,000 u/ml			
	S		U		S		U		S		U	
	D	P	D	P	D	P	D	P	D	P	D	P
17.5	4.2	1.005	3.8	.910	4.58	1.095	4.22	1.010	4.93	1.180	4.82	1.152
65.5	6.52	.806	6.17	.763	7.37	.911	6.65	.823	8.1	1.00	7.8	.965
91.5	7.4	.774	6.67	.698	8.02	.840	7.6	.795	9.3	.974	8.85	.926

D = distance of penetration. P = penetration rate. $P = \frac{D}{\sqrt{T}}$

of glycerine, deteriorate slowly but consistently at refrigeration temperature, considerably faster at room temperature, and very much faster at incubation temperature. Consequently this latter has been adopted for artificially aging pollen extracts in deterioration studies.

A ragweed extract with a potency of 60,000 units per ml, made without glycerine, was maintained in a constant-temperature water bath at 37°C. Fractions were removed and transferred to the refrigerator after nine, fifteen, eighteen, twenty-four and thirty hours. Immediately after the last fraction was removed from the water bath all five, and the unheated fraction, were poured into Oudin tubes over antiragweed serum-agar. At the same time, a series of four dilutions were made from the same unheated material and poured into another series of Oudin tubes made in exactly the same way. They were all quickly transferred to the refrigerator. Readings were taken after sixty-five hours, the penetration distances of the *b* band measured, and their rates of penetration calculated. In Figure 11 those of the dilutions are shown plotted against log concentration, and those for the heat impaired fractions are plotted on the 60,000-unit line. The dilution equivalents of the latter can be read from the corresponding penetration rates on the graph as follows:

Time heated hours	Unit value per ml
0	60,000
9	40,000
15	28,000
18	24,000
24	19,000
30	15,000

The corresponding five dilutions indicated, were prepared from the unheated 60,000-unit material, and compared with their heated equivalents by the Ouchterlony double diffusion plates (Fig. 12). It is seen that the bands of the heated and their corresponding dilution equivalents, show complete interference all through which shows qualitative identity of antigens; and the resultant arches are nearly symmetrical, except in the last, which shows almost quantitative identity. This experiment shows that impairment by incubation up to a loss of three-fourths of its potency does

not alter the antigenic structure to any considerable extent that cannot be duplicated by corresponding dilution.

The practical application of this method of standardization is shown as follows: A ragweed extract in 50 per cent glycerine, about eight months

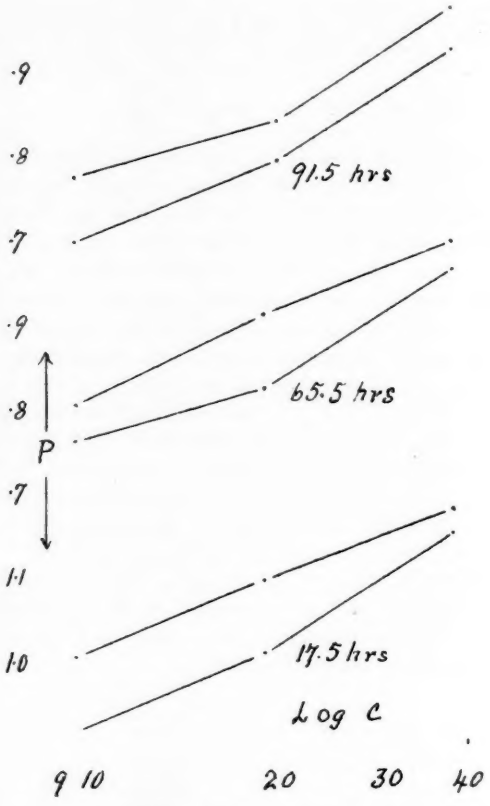

Fig. 13. Standardization. Rate of penetration (P) plotted against log concentration, at three different time intervals. S, standard; U, "unknown." Data from Table V.

old, was compared with a current standard. Three dilutions of each were made (Table V). These were laid over antiragweed serum-agar in Oudin tubes in quadruplicate. The average penetration rates are shown at three different time intervals (Table V), and plotted against log concentration (Fig. 13). The ratios for corresponding values of P at these three different times are .617, .622 and .697 or average for all three .645, indicating that the unknown has a potency of 64.5 per cent of standard.

These same two preparations were compared in two reagin neutralization tests. These showed potencies of 64 and 71 per cent. Two tests by precipitin showed 64.8 and 71.3 per cent. Thus the results of these three different methods, based on entirely different principles, agree about as closely as do the results of tests by any one method among themselves.

These data may be used to render available an *in vitro* system of standardizing allergenic extracts. It is only necessary to prepare pools of rabbit antisera for the pollens of the commoner hay fever plants. Short and tall ragweed, timothy, Bermuda grass and house dust would serve most purposes. If these are frozen and vacuum dried, they may be stored as permanent standards.

By means of a carefully selected pollen extract of average potency, the antigen-dilution graph may be established for the standard serum. This extract then becomes the prototypic antigen standard for that serum. Subsequent extracts may be titrated against it *in absentia* as long as the serum lasts. And it may be reproduced at any time it is needed by adjusting a fresh extract to its graph through the standard serum.

It has been demonstrated that pollen extracts of 100,000 units per ml or over, in 50 per cent glycerine and refrigerated, show no appreciable deterioration in a year's time. Such extracts may be prepared and adjusted through the standard antiserum to equal the prototype or at any desired fraction or multiple of it. These may be used as working standards in the preparation of commercial extracts.

For this purpose any ordinary nonstandard antiserum, rabbit, horse, human, et cetera, may be used, and any method: agar diffusion, precipitin or reagin neutralization, according to the circumstances.

It is to be hoped that the standard sera will become recognized internationally or at least nationally, and that the function of maintaining them permanently and of distributing the working antigenic standards will be taken over by W.H.O. or the N.I.H.

The details of this research will appear elsewhere.

Pearl River, New York

ARACHNIDISM

In the experience of Taubenhaus, who has tried various types of therapy in treatment of 35 patients bitten by spiders, response to cortisone is variable. Isolated instances of apparent success are probably due to the natural variation in duration of symptoms, which may last from 12 to more than 200 hours. Specific antivenin is the only adequate treatment for arachnidism.—Correspondence: Taubenhaus, L. J., *J.A.M.A.*, 152:1652, 1953.

ALLERGY (BY STEROLS?)

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Buenos Aires, Argentina

THE CUTANEOUS and respiratory, or any other localized syndromes affecting patients whose condition is aggravated during the menstrual cycle, can be caused by steroidal allergy and should be studied from this viewpoint. Zondek and Bromberg's studies on endocrine allergy first awakened our interest in this subject and following the fundamental technique recommended by them, we discovered phenomena and facts which drew us away from the theories upheld by these investigators.

For this reason, in our opinion, Zondek and Bromberg's expression "endocrine allergy" is inadequate when referring to allergic phenomena in which hormones play the role of allergens.

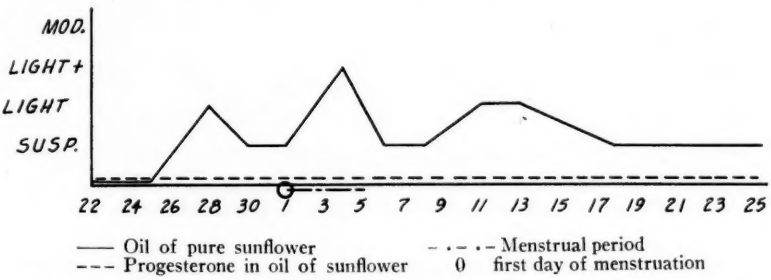
In fact, the term "endocrine allergy," corresponds to allergic phenomena localized in the internal secretory organs; it means that the shocked organ forms some part of the endocrine system. If a hormone takes the part of the allergen, then the term "hormonal allergy" should be used, and if the hormone is produced within an organ and causes a disorder within the same, it should be called "autogenous hormonal allergy."

Our first experiments were based on the work carried out by Zondek and Bromberg, and during these tests we met with what we call "paradoxical reaction," whereby the exclusive oily vehicle used as a control, occasionally produced reaction of the "recurrent type," whereas a hormone added to the oily vehicle did not. Fortunately, a conversation with Nino Marsiaj (Brazil), who had been making similar investigations, encouraged us to carry on our studies as he had also observed this paradox. This fact strengthened our idea that it would hardly be probable that an organ would allergize itself to substances which it produces of itself. That is why, when publishing our first paper on a few cases of eczema, febricula, asthma and rhinopathy, we cautiously entitled it "Probable Cases of Endocrine Allergy," and in our comments said that we had no proof that the favorable results obtained in these patients were the consequence of the reaction mechanism brought into play when giving specific treatment with allergens.

All the women studied in our experiments were within the age of sexual hormonal activity, with clinical symptoms which were aggravated before and during the menstrual period, and pre-menstrual period.

As an outcome of the publication mentioned, we made the initial hypothesis that Zondek and Bromberg's so-called "endocrine allergy" is a type of "exogenous allergy," caused by substances related to the hormones, and by virtue of this chemical relationship, occurring during the menstrual cycle, a biological reaction is let loose which we recognize as an allergic

manifestation. The allergen would be a steroidal substance which, through an ingesting or injecting medium, allergizes the organism. The hormones, appearing cyclically in the blood stream, on reaching a certain quantitative level and crossing the "tolerance threshold," would, through their chemical


MOD.
LIGHT+
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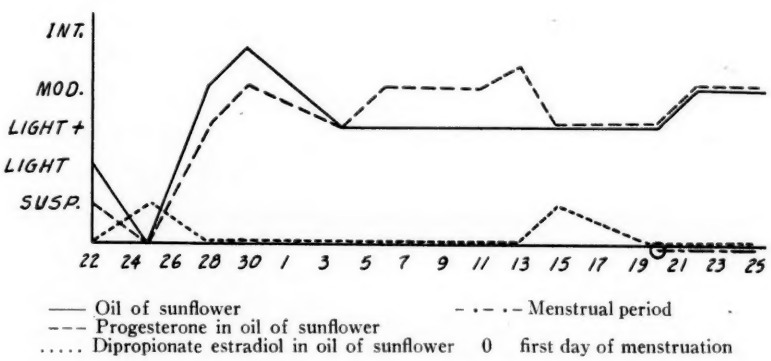
22 24 26 28 30 1 3 5 7 9 11 13 15 17 19 21 23 25
—— Oil of pure sunflower
--- Progesterone in oil of sunflower
– · – · – Menstrual period
0 first day of menstruation

Fig. 1. Diagnosis: asthma. M.J.P., aged twenty-one, single, commenced menstruation at fourteen years. Course of menstruation was 26/4 days.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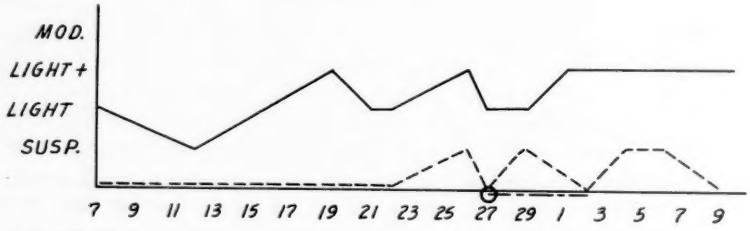
22 24 26 28 30 1 3 5 7 9 11 13 15 17 19 21 23 25
—— Oil of sunflower
--- Progesterone in oil of sunflower
..... Dipropionate estradiol in oil of sunflower
– · – · – Menstrual period
0 first day of menstruation

Fig. 2. Diagnosis: asthma. A.Z., aged fifty, commenced menstruation at thirteen years, single, course of mentruation, occurred every 3 months, 5 to 7 days. Menopause. There was a menstrual relation with the symptomology with increase of symptomology in pre-menstrual epoch; in spite of the fact that she did not have menstruation, only every three months, in the days that she ought to menstruate she had symptoms. She has now reached the menopause.

similitude, provoke the allergic reaction. These hormones would be the "loosing" substance and not the allergizing factor.

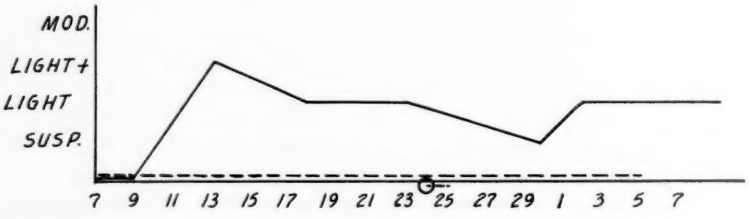
In the course of our investigations we used the following method: Intradermic cutaneous tests with sunflower, groundnut and olive oil, and the following hormones (dissolved in each of the oils): Estradiol Dipropionate, Progesterone and Propionate of Testosterone, always in the same proportion.

The site of the injection was examined periodically for one month, the "recurrent" reactions appearing forty-eight or more hours after the "test" as inflamed pruriginous papules. Each case was studied objectively by means of a system of co-ordinates. In our experience we have had cases



—— Oil of sunflower
..... Dipropionate estradiol in oil of sunflower
– · – · – Menstrual period
0 first day of menstruation

Fig. 3. Diagnosis: asthma and rhinopathy. N.E.F., aged nineteen, single, commenced menstruating at twelve years, course of menstruation was 28/5 days. Menstrual relation with symptomology; premenstrual and menstrual epoch symptomology increases.



—— Oil of sunflower
--- Progesterone in oil of sunflower
– · – · – Menstrual period
0 first day of menstruation

Fig. 4. Diagnosis: asthma. N.R.T.deC., a woman, aged thirty, married, commenced menstruating at fifteen years. Course of menstruation is 26-27 days (since 1½ years). Menstrual relation with symptomology: difficulty in breathing. Treatment with hormones was given in order to regulate menstruation. Difficulty in breathing was observed during treatment.

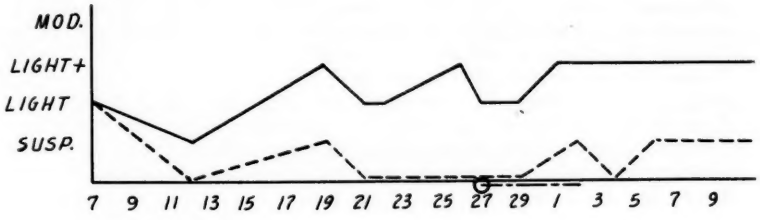
of positive reaction to pure oil and negative reaction when hormones were added to the same oil. These results do not confirm those mentioned by Zondek and Bromberg in their classic study in which the oils containing hormones gave the same positive reaction as in the cases tested with pure oil.

In the light of our own experience, the most effective skin test is the intradermic; Zondek and Bromberg's "recurrent reaction" being judged of greater importance, and rejecting the term "immediate" for reactions which we obtained forty-eight hours after the test.

Our "recurrent" cutaneous reaction gives rise to many explanatory hy-

potheses, as it is apparently the product of the antigen having been introduced twice. This does not concur with the hypothesis accepted at present in allergy and immunity.

The substance injected is an [antigen] allergen and as the result ap-



—— Oil of sunflower
--- Progesterone in oil of sunflower
– · – · – Menstrual period
0 first day of menstruation

Fig. 5.

pears after a few days it is reasonable to suppose that no pre-formed antibodies existed in the site of the injection. This leads to the hypothesis that, through the injection of the sterol, or as a consequence of it, "specific" antibodies are formed "in situ," which react by provoking a specific inflammation when a sterol or similar, or identical steroidal radical, penetrates into the blood stream.

From this hypothesis, springs the probable explanation for the premenstrual aggravation of asthma, rhinopathy, eczema, et cetera, in women in whom we could find no allergen which would account for the periodical worsening of their ailment and which was so evidently related to the catamenial cycle.

On the basis of our hypothesis, we suggest a second complementary theory: the homologous autogenous sterol would react periodically as an allergen in monthly periods, in the women who menstruated regularly, giving the "recurrent" reactions in those parts of the skin where we had previously injected heterologous exogenic sterols which could have become transformed into specific antibodies similar to autogenous sterols. This would explain how, every month, during each menstrual period, the injected sterol would exhaust itself until it completely disappeared as an antibody.

The final therapeutic test consisted of the cure or improvement by the action exclusive to the sterols under consideration, which might be related allergically, at least.

Fifty-two patients have been studied, twenty-two of whom were treated with success; twelve having completed their treatment and ten still continuing their treatment. The remaining thirty were not continued in the study because their cases did not seem to be of interest to us.

CASE REPORTS

In each of the cases we have treated with skin intradermal tests to three different kinds of oil: olive, sunflower and peanut oil, and the following hormones (dissolved in each of said oils):

Estradiol dipropionate in pure olive oil, 1 mg per cc.
Estradiol dipropionate in peanut oil, 1 mg per cc.
Estradiol dipropionate in sunflower oil, 1 mg per cc.
Progesterone in pure olive oil, 5 mg per cc.
Progesterone in sunflower oil, 5 mg per cc.
Progesterone in peanut oil, 5 mg per cc.
Testosterone propionate in pure olive oil, 5 mg per cc.
Testosterone propionate in sunflower oil, 5 mg per cc.
Testosterone propionate in peanut oil, 5 mg per cc.

Intradermic injection was done in the interior part of the arms and the skin reactions were observed every other day for a month. In this research we could make a co-ordinated system which permitted us to choose the hormones and the oils to use in each case, taking as an example, the positive reaction, until today we have not observed any one general reaction in a few hundred of these injections with oils and hormones in any one part of this work. The only inconvenience (and this is very important), was that in a few cases the injection provocated the clinic cases showing clearly the allergic reaction between the hormones and some oils used in these cases. With the same technique we studied one woman in whom we could not get any diagnosis of allergic disease.

Case 1.—A.A.deA., a married woman, twenty-one years old, whose menstrual period occurred thirty to thirty-five days, lasting for five days. She had both asthma and eczema which were worse during menstruation. Rhinitis was always present, without change during menstruation. The sensitizations with allergic tests had not been effective. There was positive reaction with the three hormones, in the three different oils. We gave special treatment with the oil of sunflower base, starting with 1/20 cc subcutaneously going up to 5/20 cc which resulted in a complete cure of all her symptoms for several months. That treatment was followed during twelve months without any premenstrual symptoms. We stopped the treatment after six months, at which time she did not have any clinical symptoms. After that she started having the old symptoms, and we began treatment, which again was one hundred per cent effective. She carried on the treatment two weeks out of every month. The dose is 3/20 cc in sunflower oil.

Case 2.—M.A.M.deC., a married woman, thirty-five years old, had a cycle of menstruation every thirty days, lasting five days. She had allergic asthma for foods, dust and bacteria, which was aggravated during premenstrual period. By eliminating certain foods to which she was allergic, and giving her the right tolerance treatment during that time, the allergic reactions disappeared except during the premenstrual period. She had positive reaction to the sunflower oil, and the three hormones in the three oil solutions. We gave her special treatment with the three oils and the three hormones, starting with 1/20 cc of each subcutaneously until 3/20 cc, and we produced typical reactions, obtaining complete cure with 1/40 cc. A few months later, the treatment was stopped, noting that there were no premenstrual reactions. Two months after the last injection, another injection, given in the same place where we

had previously given the sunflower oil and hormone, produced a typical reaction several days before her menstruation. It disappeared four days after menstruation. This was repeated once more under special circumstances in which that recurring reaction was produced in the same place as the earlier injection, and not in the place of the last injection. We followed this treatment giving her one injection every fifteen days of the three hormones, 1/40 cc because if we stopped the treatment of any one of the three hormones the symptoms recurred. She has followed this treatment for two years; four months during this time she has remained without treatment.

Case 3.—N.G.deR., was a married woman, thirty-six years of age, when menstruation periods occurred every 26 days lasting five days. She had allergy, asthma and rhinitis with menstrual and premenstrual reaction. The tolerance treatment with domestic dust and pollens (worse in spring time) brought only small results without any modification during the menstrual period. At the same time she had intestinal parasites without any breath symptoms. She had a positive reaction to the sunflower oil with the estradiol dipropionate in the same oil as well as the other two oils. We started treatment with 1/20 cc of pure sunflower oil, continued until we reached 2/20 cc when we produced one symptomatic reaction. This occurred at the same time with the reactions, in the place of the last injection, and disappeared slowly with the asthma and rhinitis symptoms. We obtained 100 per cent successful results with the lowest doses, and we stopped the treatment, but it was necessary to begin treatment again four months later. This resulted, without any symptoms, in a quick and sure cure. During one year, the day before menstruation, she had a reaction in the same place as the skin test. Observation time, one year and a half. She is still having treatment every fifteen days of 2/20 cc sunflower oil and hormones. There is now a total absence of symptoms.

Case 4.—M.deA., a married woman, twenty-six years of age, had a menstruation cycle occurring every thirty days, lasting five days. She had permanent asthma with premenstrual reaction. We could find no allergic reaction, which is the reason why we want to state that this patient has a presumptious allergy diagnosis. She had recurring positive reaction with estradiol dipropionate in sunflower and peanut oil. She was given treatment with peanut oil and estradiol dipropionate in sunflower oil solution, which resulted in a total cure. With highest doses we produced asthma symptoms. Observation time was two years. She is still being treated though she has periods of four months in which she needs no treatment.

Case 5.—L.C., a married man, seventy-three years old, had allergic asthma with emphysema. Under specific treatment with antibiotics, very little results were obtained during three years' observation. He had positive reaction with estradiol dipropionate in sunflower oil. We have given him this treatment and have obtained better results and symptomatic reaction with certain doses that we must give to him in lowest doses. We found the effective doses and all the symptoms are gone. He has been under observation for two years and is still under treatment.

Case 6.—M.L.S., a young woman, sixteen years of age, had asthma with premenstrual reaction. We could not find any allergic test reactions and with exclusive treatment of pure sunflower oil we obtained better results and finally her cure. The first menstrual period has been produced between the first month and a half of treatment and it was followed by a few symptoms. Actually, she has been two years under our observation with periods of a month in which we stopped the treatment and the patient has not had any premenstrual symptoms. Effective dosage, 2/20 cc of sunflower oil every fifteen days.

Case 7.—C.deG., a woman, twenty years of age, married, who for nine years had suffered from skin dermatoses of both hands with pruritus, and permanent symptomatology with premenstrual and menstrual reaction. We could not find any positive allergy test and we could not say whether she had an allergic dermatoses or not. All specific treatment failed. We made a skin study with oils and hormones. We started treatment with 1/20 cc of progesterone in olive oil. She followed this treatment every other day which stopped the symptoms and the reactions. She followed that treatment for a month, obtaining total recovery of her dermatoses and she is now free of all symptoms.

Case 8.—D.B., a married woman, twenty-nine years of age, who for eight years had fever in the afternoons, between 100° and 102°F., permanent, without a known cause. She had light menstrual reactions except for a slight increase in temperature over the already high rate. Menstrual pains were very regular, becoming normal with special hormonal treatment. There was no alteration in the fever during this treatment. We could not find any positive allergic reaction so that we could be sure it was allergic fever. We made clinical studies with laboratory examination and antibiotic treatment, streptomycin and penicillin, without results. We started treatment (after skin study with oils and hormones) with progesterone in peanut oil and testosterone propionate in olive oil, and after the first ten doses without any results we gave her an injection of estradiol dipropionate 1/20 and twenty-four hours later the fever disappeared as well as the rest of the symptoms. She is still under treatment, but without fever for the first time in eight years. She received treatment with highest doses, 3/20 cc. Now she has 100 per cent successful results and has been under treatment for two years.

Until such time as the possibility of the sterols being the allergizing substance is accepted unquestionably a presumptive diagnosis of clinical allergy by sterols can be made. The diagnosis is based on the clinical relationship between the aggravation of the condition and the menstrual cycle, together with the recurring skin reaction and the worsening of the condition through an overdose, the improvement or cure obtained evidently by treatment with injections of substances bearing sterols which we considered specific or at least, having a slight allergic relationship to the autogenic esteroid hormones.

In the course of our treatment we have not observed any apparent alterations either in the endocrines or the menstrual rhythm.

As for the treatment itself, at the moment, we cannot give any rules as our experience has really been over a period of only two years.

In this respect, one definite indication is, in synthesis, that we chose patients whose condition became worse before the menstrual period and after an exhaustive study of the probable causal exogenic or endogenic allergens of the syndrome or syndromes, we proceeded to investigate the presumed allergy by sterols, and on studying the system of co-ordinates mentioned previously in relation to the skin test reaction, we chose pure oil or oil with the corresponding hormone, starting the treatment with very small doses, that is, 1/40 cc until in some cases, a maximum dose of 5/20 cc was given. During the course of the treatment the local inflammatory reaction was meticulously observed with the object of not exceeding the

essential dose because of the danger of symptomatic reactions which we have already mentioned.

We also consider it worth mentioning that we have also men under treatment: one whose case report is included is being treated with female hormones in sunflower oil. This treatment favors the hypothesis of the chemical relation between hormones when treated with steroidal radicals. Nevertheless, the possibility of allergy by proteins contained in edible oils which include oil from sunflower seeds, groundnuts or olives, exists.

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ASSOCIATION OF BRONCHIECTASIS WITH ASTHMA

Though certain textbooks have contained the statement that bronchiectasis is common in association with asthma, impairing the prognosis for it considerably, reliable data on this point seem to be conspicuous by their absence. Lack of systematic bronchographic examinations of asthmatic patients may well be responsible for ignorance in this matter, and, to repair it, Dr. N. Westermark and Dr. S. Wiholm of Stockholm have undertaken bronchographic examinations of 100 consecutive patients with bronchial asthma treated at the St. Göran's Hospital since 1949. The Westermark technique was followed; about 10 ml of iodized oil (Lipiodol) was introduced after the pharynx and larynx had been anesthetized. Most of the patients had had asthma for more than 5 years, 47 of them for more than 10 years. In 18 cases, there was a history of pneumonia once or oftener, and 21 patients had had sinusitis. As many as 70 had yielded, or still yielded, purulent sputum, but genuine chronic bronchitis was present in only 5. Only in four patients was bronchiectasis demonstrable, and in each one the lesion was comparatively small, much smaller than the large and extensive lesions existing when bronchiectasis gives rise to serious symptoms. These observations suggest that asthma does not as a rule predispose the patient to the development of bronchiectasis and that the association of one disease with the other is comparatively rare. Yet in 1938, Watson and Kibler found that 90 per cent of their patients with bronchiectasis also had asthma.

PARENTERAL CRYSTALLINE KHELLIN IN THE TREATMENT OF CHRONIC BRONCHIAL ASTHMA

I. Clinical Evaluation

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INTEREST in khellin has been revived in recent years, primarily as a result of its use in coronary artery disease and the anginal syndrome.[1,3,4,8] Anrep *et al*[1] demonstrated that the drug possessed coronary vasodilator action. Based upon the work of Samaan,[13] these investigators believed that khellin relaxed smooth muscle in general, and particularly that of the coronary vessel wall. Samaan had shown relaxation of smooth muscle also in the ureter, intestine and bronchus. Anrep and his co-workers[2] followed this up with a study of asthma, based upon the bronchodilator action of the drug. Kenawy *et al*[9] extended these observations to 138 cases. After interest had been evoked in this country, several groups of observers[6,7,11,12] reported the results of treatment of bronchial asthma. Their conclusions were, in general, favorable to continued use of the drug in asthma, whereas no such unanimity of opinion characterizes the results of use in angina. In reports dealing with asthma as well as with angina, the problem of side effects became the chief stumbling block to further study of these cases. Hultgren *et al*[7] were the latest to comment on the high incidence of reactions with oral administration of khellin. They pointed out the important fact that the side effects can be largely overcome by parenteral administration, though local pain was severe in some cases given their particular preparation.

This study was designed to test the side effects produced by a new intramuscular preparation of khellin, and to obtain an indication of its practical value. It is considered a preliminary report primarily because the clinical observations are subjective.

The material used is a suspension of crystalline khellin in sterile isotonic saline so that 50 mgm are contained in 1 cc.* Since one observer reported the toxic effects to be due to the less effective visnagin and the ineffective khellol glucoside, only pure crystalline khellin was placed in this suspension. Being a suspension, rapid absorption would not be expected. Instead, long-continued slow absorption, and consequent lengthening of any beneficial effect, should be anticipated. Thus, in treating a patient in an acute attack of asthma, the physician would have a weapon against the chronic bronchoconstriction, and against the recurrence of symptoms within a few minutes to a few hours following the administration of other bronchodilator drugs. Some asthmatic patients present perennial and chronic symptoms, and report some wheezing during some part of every day throughout

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**Ammivin Injectable;* supplied through the courtesy of the Medical Research Department, The National Drug Company, Philadephia 44, Pennsylvania.

TABLE I. CLINICAL EFFECT OF KHELLIN ON CHRONIC BRONCHIAL ASTHMA

	Unimproved	Slightly Improved	Moderate Improvement	Total
Demonstrable Emphysema	1		2	3
Chronic asthma without demonstrable emphysema	4	4	26	34
Total	5	4	28	37

the active phase of the disease. This type of patient is frequently resistant to both symptomatic and allergic management and stands to benefit most from a drug which has a long period of activity. A pilot study revealed that such patients experienced relief from intramuscular crystalline khellin suspension to a greater degree than other asthmatic individuals. The present study was confined almost entirely to the chronic asthmatic. Side effects and clinical status are then the subjects for discussion in this group.

RESULTS

The results, summarized in Table I, indicate that khellin, administered intramuscularly, exerts a significant effect upon the symptoms of chronic bronchial asthma. As would be expected, the majority of the patients studied were over thirty years of age, though one chronic asthmatic child, aged eight, is included. The dosage varied from 50 to 100 milligrams each injection with no attempt being made to correlate the higher dosage with ultimate effect. To a group of forty-five patients, 296 injections were given either once or twice weekly. Eight patients received only one injection. Correction for the removal of the latter group from the study leaves thirty-seven patients in whom the disorder could be followed sufficiently long to permit reasonably valid conclusions.

Control studies were set up with three patients by substituting the same amount of buffered saline in the same type of syringe and using the same length and bore needle. The patients reported benefit only when khellin was given and not when the buffered saline was injected. Care was taken to select for control only those patients who felt no local soreness from the injection, since they might be able to recognize the saline by noting this effect. As a further control a period of time was allowed to elapse, during which the asthmatic symptoms gradually returned. When the crystalline khellin was injected under these circumstances, the effect on those patients who were previously relieved was immediately noticeable. This procedure was followed in an additional eight patients.

Relief of wheezing was noticed by the evening of the day of injection and persisted for three to five days in those cases favorably affected. When the effect by the evening of the day of injection was minimal or absent, no additional help could be expected. No permanent effect was noticed in any patient, for asthma returned in each case when injections were discontinued.

SIDE EFFECTS

Slight nausea developed in only one patient, which could not be evaluated further since he was not seen again for further therapy. Of the thirty-seven patients who were followed long enough, none reported nausea or other gastrointestinal disturbances. In seven patients local pain or soreness developed, which was insufficient to cause a change in dosage or frequency of injections. The local effect did not prevent activity of the injected limb of these patients.

DISCUSSION

Search of the literature failed to reveal descriptions of the types of preparations used for parenteral administration, except for the papers of Lian and Charlier[10] and of Hultgren *et al.*[7] Early workers reported khellin used in the form of tincture for oral administration, and decoction for introduction locally into the ureter. Anrep *et al*[2] used a solution of 60 mgm/cc and of 50 mgm/cc for intramuscular use, but failed to report the vehicle. Lian and Charlier[10] gave an excellent description of the drug, particularly as regards poor solubility in water or isotonic saline solution. Hultgren and his co-workers[7] used a solution of 50 mgm of khellin in olive oil and ethylacetate for intramuscular administration, and a 30 mgm/cc preparation in a 40 per cent solution of sodium benzoate for intravenous administration. Queries directed to the manufacturers sponsoring other studies, showed the intramuscular preparation to be a solution in ethylene glycol. These solutions were apparently used by Barsoum *et al*[5] in their report of the rapid absorption and slow excretion of khellin injected intramuscularly.

Failure to find significant toxic reactions or serious side effects from a drug administered parenterally, as opposed to these reactions occurring from the same drug given orally, indicates that the cause of these difficulties is by a direct effect upon the gastrointestinal tract. Thus, finding of negligible side effects from this preparation of injectable pure crystalline khellin can be used as evidence for direct gastric irritation when the drug is taken by mouth. The pattern of these side effects is not at all uniform when reports of different investigators are compared. One manufacturer states that the incidence of these reactions varies from 20 per cent to 80 per cent with his preparation. Such a variation can only mean an unpredictable individual susceptibility to this direct gastrointestinal effect. Our patients were purposely not studied with oral administration, primarily because this mode of administration could not be properly controlled. Subsequent extensions of this problem should involve a comparison between oral and parenteral methods in the same patient, particularly in those who report gastrointestinal symptoms from oral administration.

The relation of the side effects to dosage remains a difficult question to solve. Certainly our results demonstrate the fact that a much larger amount of drug can be administered intramuscularly than can be given orally without side effects.

Incidence of the chronic asthmatic patient, in relation to the total number of asthmatic individuals, is difficult to ascertain. There are, however, a sufficient number of these patients in the practice of most allergists to warrant further interest in injectable pure crystalline khellin as a tool for symptomatic relief. These patients present problems requiring investigation along allergic as well as non-allergic lines. Frequently, drugs presently available do not suffice to control symptoms. Injectable pure crystalline khellin may well be a means of helping the patient, while investigation is under way and the long-range program is taking shape.

SUMMARY AND CONCLUSIONS

An aqueous suspension of pure crystalline khellin was administered intramuscularly to forty-five patients. This preparation differed from those previously reported in the literature, which have been solutions in an appropriate solvent.

In contrast to the severe local pain reported for other intramuscular preparations, the suspension caused only mild local pain in seven subjects.

Gastrointestinal upset was reported by only one patient, who did not return after a single injection, in contrast to the high incidence reported for oral administration of khellin.

As a preliminary report on clinical effectiveness in patients with chronic asthma, subjective data are included in this report indicating appreciable degrees of benefit in twenty-eight out of the thirty-seven patients of the group who received more than one injection of the crystalline khellin.

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EMOTIONAL ASPECTS OF PEDIATRIC ALLERGY—THE ROLE OF THE MOTHER-CHILD RELATIONSHIP

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THIS REPORT originated from our association with the Out-Patient Clinic for Pediatric Allergy, Colorado General Hospital, a teaching hospital of the Colorado University Medical School. We became interested a few years ago in this particular aspect of pediatrics when we noticed that the mothers and their children reported almost religiously week after week for their "shots," often having to wait a considerable period of time and at the same time complaining about it rarely. We "felt" the presence of psychological factors, and expected that their recognition and possible handling might contribute to an increased understanding of the allergic problems.

We would like to point out that this paper is not written to take a stand on the question of which is primary—allergic or emotional factors. We view emotional components as an aspect of the allergic patient, in addition to the well-established and supported science and practice of allergy. We believe it important to evaluate the respective merits of allergic and emotional factors in each individual case. Our study shows that emotional factors can be easily observed and demonstrated in these cases; their recognition and treatment may lead to more satisfying results.

The material of this study consists of twenty-two children with allergy. There were eleven boys and eleven girls, ranging in age between two and fifteen years, with an average age of 9.2 years. The allergic diagnoses included twelve cases of asthma, eight cases of allergic rhinitis, and three of eczematoid dermatitis. (One patient suffered from both asthma and eczema.) This distribution did not permit us to draw conclusions about allergic reactions in general, as we had hoped, but only about respiratory allergies.

These children had been referred to the Pediatric Allergy Clinic from the Pediatric Out-Patient Department where they had previously been examined. Only those were referred for whom symptomatic treatment alone had been impractical or unsuccessful.

The clinic was staffed by a pediatric allergist, a nurse, and a medical

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technologist who jointly examined, tested, and treated according to recognized immunological methods. In addition, a medical social worker, a psychologist, and a psychiatrist were assigned to the clinic. Although there was considerable overlapping, the functions of the members of this team were divided as follows: the social worker would obtain a social history from the mother, and, if available, also from other sources. The psychologist gave each child a series of psychological tests which were designed to evaluate the child's innate intellectual and emotional abilities, as well as to gain some understanding of his conscious and unconscious thought processes. The psychiatrist tried to obtain an impression of the personalities of the mother and the child, usually in separate interviews.

Following these separate investigations, we held a conference on each case, to which the staff of the Allergy Department was invited. These conferences aimed at a mutual exchange of information and a recognition of significant factors. A report of the combined thinking was incorporated in the patient's clinic file together with recommendations.

We were interested in a previous statement by Rogerson,[7] that allergic children often are found in a position of special significance in the family constellation. This was often confirmed in our series.

Two of the children were the only child in the family; nine were oldest in families of between two and four children; five were the youngest in families of three to nine children. Discounting three in families of two, we have in this group thirteen children who were either the only, the oldest, or the youngest child. Among the remaining children, two were the only boys in the family; two were deliberately planned by a mother to save a psychologically impossible marriage; one was a first child in a second (also unsuccessful) marriage of the mother.

The next item of interest was the mothers' ages at the time the allergic children were born. Although these ages ranged from eighteen to forty-five, the distribution showed a bi-modal curve with an almost free interval between the ages of twenty-six and thirty-six. (Fig. 1)

All mothers impressed us as being very capable and competent; at the same time they felt threatened if they were not masters of the situation. It seemed to be quite apparent that in practically all cases the mother was the guiding and dominant person in the home.

All the mothers showed open concern and great anxiety with regard to the allergic manifestations of their children. An underlying attitude of rejection, either conscious or unconscious, could be readily discerned. (This coincides with other studies, predominantly those by Baruch and Miller[4] and Gerard.[2])

We noticed, however, a special aspect of this rejection. We first became aware of it by frequent differences between the impressions of the social worker and the psychiatrist about the same mother. The social worker might have evaluated her as a warm person, while the psychiatrist, seeing her at another time, felt she rejected her child and was not affectionate.

At other times these impressions were reversed. Although we were at first inclined to attribute this discrepancy to inadequate techniques, we later recognized that the mother's attitude towards her allergic child was not a constant one but one of periodic variations; the mother's feelings oscil-

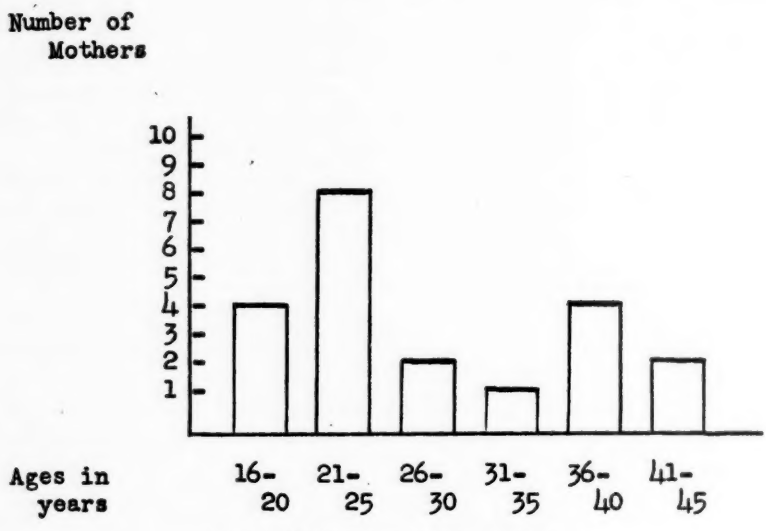

Fig. 1. Mothers' ages at birth of child.

lating between outright or concealed hate to one of utmost concern and solicitude.

The mothers' efficiency appeared more outstanding when their husbands were considered in the study. We had the strong impression that the mother proverbially "wore the pants in the family." While in only one of the twenty-one families involved, the real mother was dead, in five families the real father was dead, or had left through divorce or separation. There was evidence of prolonged parental separations in three other cases. Two fathers were chronic alcoholics. One was an overt homosexual and a cripple since childhood. Four fathers were suffering from disabling illnesses. Two fathers had hay fever and asthma. Of the three step-fathers, one was extremely passive; one had been married to the mother only a short time and the marriage annulled because of polygamy; one was committed as criminally insane. Three fathers were found to be undemonstrative in their feelings. There was evidence of gross social, educational, and sexual inferiority on the part of the father in four additional cases.

The argument might be broached that the paternal weakness may be related to the fact that these were medically indigent patients. Neverthe-

less, two additional observations seemed to give added weight. One is the rather forceful personalities of the mothers, the other is that most of the mothers displayed a high degree of sexual frustration and dissatisfaction—a factor which does not necessarily go along with a low economic level.

A surprising observation was the fact that most of the mothers easily recognized and described the emotional problems of their allergic children, and the relationship it bore to them. This was apparent on casual interviews with the mother whether the interrogator was a psychiatrist, a social worker, or a pediatrician. Many mothers spontaneously described in detail emotional problems which they had recognized; they referred to the allergic manifestations only on direct questioning. This contrasted to our experiences with adult psychosomatic patients, who are notoriously able to talk about their somatic manifestations, but often resist the discussion of their emotional symptoms.

The mothers often considered their children too active and aggressive, and believed it their task to control them. It appeared to us that the mothers' innate needs to restrain their children went far beyond that necessitated by the allergic manifestations and the physician's advice. The mothers often complained, and quite obviously felt, that they were unable to successfully maintain this control. They asked questions and help from the interviewer about how to better proceed in that direction.

A similar observation was made in a number of the interviews with the children. To inquiries about their complaints or their reasons for coming to the clinic, they might talk about behavior and disciplinary problems, about their experiences in treatment, and often only as a last item, about their allergic symptoms. These seemed to be of considerably less importance to them than to the mother. The discrepancy between the anxious complaint of the mother and the indifference of the child was striking.

This brings us to the observations of the children themselves. Most of the following findings were obtained through psychological tests which were fairly standardized. As far as feasible, we administered the Wechsler-Bellevue Intelligence Test, or the Wix-Modification test for small children, the Thematic Apperception Test, the Rorschach Test, and Family Drawing Test.

Findings previously obtained by Rogerson and others,[7] of above average intelligence, were not confirmed. Our group showed an average intelligence, with individual variations from low normal to superior. This coincides with findings cited by Chobot.[1] In several children, a marked inhibition of motor expression was noted; this was especially true of the younger boys. All children showed much stronger emotional ties towards mother than towards father. Nevertheless, they regarded the mother with ambivalance and unconscious fear. They viewed her as alternating between extremes of seduction, overconcern, and intolerant rejection. There was evidence of more than usual hostility towards the mother which was generally unconscious and not permitted to be openly expressed. (Compare

Miller and Baruch[5]) A number of the children had turned this hostility towards themselves rather than outwardly. These children, consisting of older girls, showed evidences of mild or moderate depression. It seemed that this inability to express resentment was in close relationship to a fear of rejection by the mother. A group of four older girls showed notable hysterical manifestations. They were affectively labile and had a need to sexualize their enviroments. This was sometimes also expressed in a seductive attitude towards the examiner.

Rather consistent, as well as quite instructive, were the findings on the "family drawings." They demonstrated unusually strong, unsatisfied oral dependent cravings in the child. Similar immature cravings were projected on the parents and siblings too, to the point where the separate members of the family seemed to follow a stereotyped, rigid pattern, as was shown in a series of drawings made by the children studied. The absence of hands and arms seemed to indicate the fear of motor expression.

COMMENT

These observations may give us an additional insight into some of the psychological processes frequently existing in allergic children. In psychological medicine, rejecting and overprotecting mothers have been recognized and described in relation to different emotional problems of the children. The mothers of allergic children seem to occupy a special rôle by their periodic oscillation evidenced in their relationship to the child. It seems significant that most allergies run a somewhat periodical course.

Although we do not have adequate statistical material to substantiate it, we would like to offer the following psychological hypothesis. We find mothers of allergic children in a general sense to be frustrated, in an expression and acceptance of certain basic needs, by living with a relatively weak husband; this, however, may not necessarily apply to husbands in the higher stratum of society. These needs will try to seek other outlets, and therefore are easily centered on a child, who, for some reason, is of special importance to the mother.

However, in spite of his ever increasing efforts, because the child is only a child, he is not capable of any real gratification for the mother, but rather leads her to an increasing state of frustration. The mother, in her state of frustration, is seeking other solutions for her feelings, and "in desperation" will consider the child responsible for her state of affairs. The mother becomes threatened and annoyed, reacts with an attitude of pushing away and rejecting the child.

The child experiences anxiety and fear of losing his mother's love. Particularly, because of his great efforts in attempting to please the mother, the child has difficulties in expressing his fears and discontent directly; he is afraid of being further rejected by his mother. One way in which he can express such feelings is through his allergic manifestations.

The somatic manifestations arouse mother's anxiety and sympathy. At

this point the cycle is ready to begin anew. The mother has given her love to the child and is ready to expect some gratification in return. The child feels guilty for having been loved, in the face of his weak and angry reaction towards mother, and is ready to do his best to please her. This theory helps explain the periodic nature of the allergic manifestations from a psychologic point of view.

As stated in the beginning we do not question the existence and the importance of the allergic facts. However, our observations make one wonder, if by paying attention to these factors alone, we do not ignore other conditions which may also be of importance for the allergic child. We have come to think in terms of subclinical allergy, which when combined with subclinical psychologic factors, produces the picture of the manifest clinical allergy. In psychiatric thinking, for example, we have long been aware of the existence of disturbances in a subclinical form which produce symptoms only when combined with additional traumatic factors.

With the exception of two, none of the children described in this series showed clinical signs of overt gross psychological disturbances. However, we believe that in our cases, a combination of allergic and emotional factors was responsible for the allergic symptoms as we saw them.

We would like to end this report with some remarks about therapeutic implications. Peshkin[6] and Hurst et al[3] have pointed out the surprisingly beneficial results of separation of children with intractable asthma from their natural parents. Although we do not feel that such drastic measures are indicated in any but the most extreme cases, we believe, nevertheless, that the mother, as a responsible parent, is of such great importance that she should be considered as an integral part in the treatment plan rather than only as a source of information when she accompanies the child to the clinic.

We feel that adequate and comprehensive treatment of an allergic child should involve an approach on allergic and emotional levels involving both the child and the mother. We are sure that every practicing allergist uses "psychology" in his patient-physician relationship. Discussing history and treatment of the allergic child, he has spent long periods of time with the mother, thereby giving her considerable support. He has, by the chronicity of the treatment, introduced himself as a constant and stabilizing factor into the mother-child relationship, possibly fulfilling some of the needs that were expected to be gratified by the father and husband. The mother, witnessing the child's repeated injections, might interpret them as punitive acts and thus might feel that the clinic concurs with her needs to reject and punish the child. Some of the mother's needs may thus be accepted or gratified with advantage for the child rather than to his detriment.

We have learned from others and our own experiences that a direct psychiatric approach to these patients is difficult and often unrewarding. One may attribute this to our lack of experience and clear concept of treat-

ment principles in these cases. But we feel also that a large rôle is played by the difficulties which the allergic sufferer has to consider and accept separate emotional treatment. These patients resist the splitting of their emotional problems from their somatic manifestations.

CONCLUSIONS

1. We found the mothers of our allergic children to be relatively and absolutely rather strong, active, and anxious, with a great need to be in control. By relatively, we mean in comparison with a psychologically weak father.

2. The position of the child in the family was "special"; he was either on an "exposed" spot among his siblings, or for other reasons occupied a rôle of particular importance to the mother. These children were born outstandingly in the beginning or towards the end of the mothers' child-bearing period. This has been statistically the most striking data of our series.

3. There was a periodic oscillation of the mother's attitude towards the child, changing from extreme concern and overprotection to one of intolerant and impatient annoyance.

4. The children of both sexes showed much stronger identification with the mother than with the father. Younger children showed a noteworthy inhibition of motor activity; while older children, particularly girls, showed symptoms of emotional depression and hysterical manifestations.

5. Throughout, the children showed great ungratified dependency needs, and at the same time unconsciously portrayed their parents and other family members as equally frustrated persons from whom they could expect and receive little gratification.

6. It is our belief that in general the allergist or pediatrician is in a much more advantageous position to supply emotional support and insight with his therapy. Only the exceptional case in which psychologic problems are overwhelming may require the handling by a psychiatric specialist.

7. Much anxiety of the mother can be alleviated by the allergist, during initial and subsequent visits, by understandingly inquiring into and accepting the mother's concern and problems in relation to the child. Such an interest in itself is reassuring, but more so if combined with an attitude and a conveyed impression that these factors are often found in connection with and related to allergies. The allergist may profitably show a personal interest in the child and become a counter-balancing factor when mothers' need to control becomes excessive. Wherever feasible, a joint approach with a psychiatrically oriented social worker, a psychologist, or a psychiatrist may be an interesting and mutually rewarding experience.

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DISEASE-FREE "ISLANDS"

Disease-free "islands" are one of the greatest mysteries unsolved by modern science, according to Dr. Eugene H. Payne of Parke, Davis & Company, a leading authority on tropical diseases.

Speaking on the General Electric Science Forum over radio station WGY, he pointed out that even though it is surrounded by malaria-infested areas, one Brazil town of 15,000 people has been absolutely free of this disease for at least a century. A number of the land-islands free of disease have been found in South America. Some of these areas are void of heart disease and hookworm though adjacent sectors report many such cases. Similarly, insanity is practically unknown to Bolivians. Many theories have been developed as to why this immunity exists, but none has as yet been proven.

Dr. Payne stressed the importance of studying these remote peoples while they remain static. Once they mingle with other groups, science will lose its chance to determine how they remain free from diseases which infest regions around them.

INTRAMUSCULAR PHENERGAN
Preliminary Report

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SINCE the introduction of the antihistaminic drug Phenergan by Halpern, of France, in 1946, several papers have appeared concerning its use in tablet form by mouth. On this continent Waldbott, Peshkin, and Silbert have published reports. Their opinions seem to corroborate those of various European workers, to the general effect that Phenergan is a very potent antihistaminic drug with prolonged action. To quote Silbert,[3] "The unusual effectiveness and low toxicity of Phenergan established a definite place for it in the armamentarium of the physician."

Ampoules of Phenergan (2 cc) containing 50 mg of Phenergan for deep intramuscular use have been available in Canada for a number of years. It is the writer's understanding that a similar preparation of Phenergan will soon be available in the United States. The author has used this Phenergan intramuscularly in a small number of cases of asthma. A report of his experiences with it may prove of value.

In a few cases Phenergan intramuscularly has given no relief or very little relief to the asthmatic patient in a severe paroxysm. This seems to be in particular those in whom the asthma is associated with a considerable degree of bronchitis with purulent sputum.

In the majority of asthmatics the drug has proved to be extremely valuable, particularly in the type of case which has become over-stimulated by repeated doses of adrenaline. In several cases of this type the author has found it possible to stop adrenaline abruptly and maintain the patient for a number of days in much greater comfort by administering 50 mg Phenergan intramuscularly twice or at most three times in twenty-four hours. This is interpreted to be due in part to the pronounced sedative effect of the drug as well as to its antagonism to histamine. In some it was found possible after four or five days of intramuscular medication to keep the patient comfortable with 25 or 50 mg of Phenergan by mouth once or twice a day. Peshkin's statement[2] applies with even more emphasis to the ampoules than to the tablet, "If the patient is ambulant, than it becomes mandatory that Phenergan be administered only before bedtime."

This paper is not a statistical report. In addition to the cases where Phenergan has been used occasionally as a means of obtaining relief with sedation in isolated asthmatic attacks, the author has employed Phenergan as a means of controlling severe and continuous asthma of long duration in seven cases. Brief descriptions of several cases serve to illustrate.

Case 1.—C. L., a sixty-eight-year-old man was first seen April 28, 1951, because of intractable asthma for many months, using 1 cc doses of adrenaline about every four hours, or as much as ten 30 cc bottles a month. The patient was hospitalized and the adrenaline discontinued entirely. He became much more comfortable on one

2 cc ampule of Phenergan intramuscularly every night for about ten days and some syrup of chloral hydrate as an additional sedative. Thereafter he had one 25 mg tablet of Phenergan each night. His sinuses were considerably blocked and he had much muco-pus draining down his nasopharynx. He was given a course of *Hemophilus influenzae* Serobacterin Vaccine Mixed, as described elsewhere by the author[1] He had considerable bronchiectasis and ran some temperature from time to time. He had two short courses of Aureomycin by mouth. On May 19, he was considered well enough to go back to his home in the country and receive follow-up treatment from his family doctor. March 9, 1953, a friend reported this patient was doing well.

Case 2.—P. H., a sixty-two-year-old woman had been hospitalized many times with attacks of bronchial asthma and also had definite myocardial damage as shown by electrocardiogram. She was admitted to the hospital March 12, 1953, and placed in an oxygen tent. The author was consulted March 14. The asthma had responded only slightly to intravenous aminophylline, subcutaneous adrenaline, and oxygen. There was some delay in obtaining Phenergan for intramuscular use but she received her first inoculation of 2 cc at 10:30 p.m. March 16. The nurses recorded that she had "a fair night." Thereafter she received 2 cc Phenergan each night and morning. Oxygen was discontinued on March 18, and on March 19, 20, 22, she required the Phenergan only once a day. After March 22, she required no more palliative treatment for the asthma. On March 19, she was started on a course of *H. influenzae* Serobacterin Vaccine Mixed. On March 28, she was up walking about the room to some extent and received her fourth injection of *H. influenzae* Serobacterin Vaccine Mixed. On March 29 she was discharged to her home.

Case 3.—If one can judge from the case of Mrs. S., Phenergan is not accumulative, toxic, or habit forming when used for a long period of time. This patient received her first relief from a longstanding bout of asthma on New Year's day, 1948. Other treatment changed her from a chronic invalid to a reasonably healthy and active woman who had occasional isolated attacks of asthma. She has used Phenergan quite freely for over five years, averaging about ten ampules a month. She uses it only at night if she feels she is developing a slight wheeziness. Early in 1953, when she was under very severe emotional distress on account of the critical illness of her husband she avoided respiratory embarrassment by using 2 cc Phenergan each night for about two months. As soon as the emotional stress was less she required very much less frequent doses of Phenergan. In the five and one-half years this patient has received approximately 600 ampules of Phenergan.

The author has had very little experience with intramuscular Phenergan in allergic cases other than asthma. In a personal communication, Dr. M. Murray Peshkin authorized the statement that in a few cases with severe urticaria and angioedema (accompanied by a nervous state amounting almost to panic) when all other antihistamines failed by oral route he found an injection of 25 mg Phenergan solution at twelve-hour intervals "not only gave dramatic relief of the dermatoses but also induced prolonged and grateful sleep and relief from the profound emotional disturbance."

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CHEMICAL AND PHARMACOLOGICAL CHARACTERISTICS OF THE ANTIHISTAMINIC COMPOUND, PYRROBUTAMINE

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THE FIRST of the antihistaminic drugs became available less than a decade ago. Since that time research has been directed at synthesizing a histamine antagonist which would exhibit higher potency, combined with lower toxicity and more prolonged action, than antihistaminics now in common use. After several hundred compounds had been prepared, pyrrobutamine* was selected as the one which most nearly met the requirements. It is our purpose at this time to enumerate some of its chemical and pharmacological characteristics.

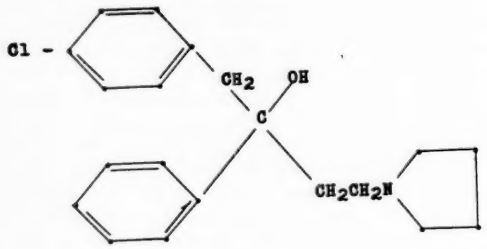

Fig. 1. Amino Carbinol.

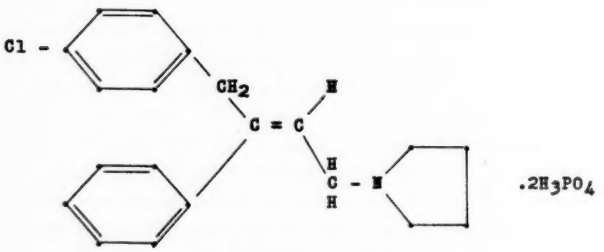

Fig. 2. Pyrrobutamine.

CHEMISTRY

Pyrrobutamine is the diphosphate of 1-*p*-chlorophenyl-2-phenyl-4-pyrrolidino-2-butene. Antihistamine drugs have been classified,[1] according to chemical structure, into derivatives of (a) ethanolamine, (b) ethylenediamine, (c) pyridindene, (d) aminopropane, and others. Pyrrobuta-

*"Pyronil" (Pyrrobutamine, Lilly).

mine is an allyl amine and differs structurally from any of the other classes of antihistaminics that are at present marketed.

Pyrrobutamine is prepared by the dehydration of amino carbinol (Fig. 1) under acidic conditions.

The graphic formula of pyrrobutamine is shown in Fig. 2.

The amino carbinol (Fig. 1) is essentially devoid of antihistaminic action. Its dehydration leads to a mixture of isomers of the "cis" and "trans" forms of the 1,2 and 2,3 butenes. Of the four possible isomers, pyrrobutamine was found to be the most stable, and it alone exhibited high antihistaminic activity.

Approximately forty variants of the basic structure were prepared, but pyrrobutamine was the only one which, in pharmacological studies, exhibited high potency per milligram, combined with prolonged activity and low toxicity. When the para-chlorine atom on the benzene ring was replaced by hydrogen, the resulting compound was found to have high potency but short activity. Reduction of the double bond between the carbons yielded a butane derivative with low activity. When the pyrrolidino group was replaced by other amino functions, the resulting compounds exhibited lower potency and shorter action.

The diphosphate salt is a white crystalline solid, melting at 128° C. It is soluble in water. Ten per cent solutions can be prepared readily. In the early investigations, the hydrochloride salt was submitted to clinical trial. It was, however, less soluble than the diphosphate salt, and, in some cases, appeared to be absorbed inadequately.

PHARMACOLOGY

It is well known that if an isolated strip of guinea pig ileum is immersed in a solution of histamine, the ileum shortens due to contraction of smooth muscle, but that if the ileum is previously dipped in a solution of a potent antihistaminic compound, the contractile stimulus is depressed. Three of us[2] have reported that if the ileum was first immersed in a bath containing 0.005 to 0.010 micrograms of pyrrobutamine per cc, and then in a solution containing 0.5 micrograms of histamine per cc, the contractile response to histamine was reduced 50 per cent. The activity of pyrrobutamine in this experiment was approximately fourteen times as great as that of diphenhydramine. Moreover, the pyrrobutamine effect persisted in the strip of ileum for a relatively long period of time in spite of repeated immersions in the histamine solution. It appeared from this that perhaps pyrrobutamine did not readily wash out of the tissues and that it might, therefore, exhibit prolonged clinical action.

PROLONGED ACTION

Guinea pigs were placed in a chamber through which an aerosol mist of a 1-per cent solution of histamine acid phosphate was passed at a constant rate. The same chamber and the same standard aerosol mist were

TABLE I. ORAL ANTIHISTAMINE ACTIVITY IN GUINEA PIGS SUBJECTED TO A HISTAMINE AEROSOL

Drug	ED_{50}±S.E., mg./Kg.	Minimal ED_{100} mg./Kg.	ET_{50}±S.E., hours
Pyrrobutamine	0.79±0.125	2.75	13.3±0.55
Chlorcyclizine HCl.	2.31±0.53	10.0	6.5±0.22
Chlorprophenpyridamine maleate	0.6 ±0.19	1.4	2.8±0.31
Tripelennamine HCl.	3.23±1.26	20.0	4.1±0.51
Thenylpyramine HCl.	5.5 ±0.99	36.5	3.5±0.57
Diphenhydramine HCl.	16.48±2.2	70.0	8.1±0.44

used for all animals. All of the guinea pigs used in the test had shown, within three minutes after entering the histamine aerosol, definite signs of dyspnea which resulted in a gasp. As soon as the gasp appeared, the animal was removed from the chamber and saved for future experiments.

It was known that if enough antihistaminic drug was administered to one of these animals, it could then remain in the histamine aerosol for three minutes without evidence of dyspnea. Accordingly, groups of five to ten animals were given various oral doses of pyrrobutamine until a median protective dose (ED_{50}) could be calculated. Similarly, the minimal effective dose that protected *all* animals of the group (ED_{100}), was determined. It will be seen from Table I that the median protective dose (ED_{50}) was 0.79 ± 0.125 mg per Kg., and that the minimal dose protecting all animals (ED_{100}), was 2.75 mg per Kg. In a similar manner, the effective oral doses of five other antihistaminics were also determined.

Groups of animals were then given the dose designated as ED_{100}, and were placed in the histamine aerosol chamber for three minutes at intervals of one hour, until the effects of the drug had worn off sufficiently so that evidence of dyspnea was exhibited within the three-minute period. The median time for return of histamine sensitivity was calculated for each drug and is designated in Table I as ET_{50}. Under the conditions of this experiment the ET_{50} of pyrrobutamine was calculated to be 13.3 ± 0.55 hours. Of the other drugs, Diphenhydramine Hydrochloride exhibited the longest ET_{50}, which was 8.1 ± 0.44 hours following a dose of 70 mg per Kg.

These figures suggest relatively high potency of pyrrobutamine per milligram and a prolonged period of effective action.

As to toxicity, the median lethal oral dose of pyrrobutamine for guinea pigs was found to be 992.6 ± 107 mg per Kg. This may be compared with 0.79 ± 0.125 mg per Kg which was the median effective dose in this experiment.

NON-ANTIHISTAMINIC CHARACTERISTICS

Pyrrobutamine was investigated for possible anesthetic, fungistatic, and bacteriostatic activity.

Local anesthetic action was demonstrable following intracutaneous injec-

TABLE II.

Compound	Concentration of Solution	Duration of Local Anesthesia	
		Eyes Topical	Skin Intracutaneous
Pyrrobutamine	0.25%	none	58 min.
Pyrrobutamine	0.5 %	35 min. (slight)	121 min.
Pyrrobutamine	1.0 %	92 min.	7 hrs.+
Thenylpyramine	0.25%	none	56 min.
Thenylpyramine	0.5 %	none	124 min.
Thenylpyramine	1.0 %	17 min.	7 hrs.+

tion in guinea pigs, and also topical application in the eyes. Table II gives a comparison of pyrrobutamine with thenylpyramine. It will be seen that pyrrabutamine had greater anesthetic effect than thenylpyramine following topical application in the eyes, but that when the drugs were given intracutaneously their effects were approximately equal in the concentrations used.

The fungistatic activities of pyrrobutamine and two other antihistamines were tested. At a concentration of 0.2 mg per cc, pyrrobutamine inhibited the growth of *Trichophyton interdigitale*. Concentrations of 1 mg per cc inhibited *Trichophyton rubrum* and *Candida albicans*. Thenylpyramine, in the same concentrations, exhibited no fungistatic effect against these three organisms, but chlorprophenpyridamine maleate showed approximately the same activity as pyrrobutamine. None of the three compounds was fungicidal in these concentrations.

To investigate the bacteriostatic activity, a culture of *Streptococcus pyogenes* C203 was used. Inhibition of this organism was produced by a concentration of 25 micrograms of pyrrobutamine per cc. It was estimated that a systemic dose of 15 mg of pyrrobutamine could not be expected to produce in an adult human a serum concentration of more than 1 microgram per cc. Hence, systemic administration of this drug could not be expected to exert significant antibacterial activity. The possibility that topical application might be effective has not yet been investigated.

SUMMARY

Chemically, pyrrobutamine differs from other available antihistaminic compounds.

Pharmacological observations suggest that it is a potent antihistaminic drug with low toxicity and prolonged action.

Local anesthetic, fungistatic and bacteriostatic activities are reported.

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METAL SENSITIVITY IN ECZEMA OF THE HANDS

Degree and Range of Sensitivity to Chromium and its Compounds

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METAL CONTACT dermatitis is seen often enough to warrant continual suspicion of its etiology in dermatoses. Usually, an eruption from metal is easily detected, such as jewelry sites—ear lobes, neck, wrists and fingers—also back of ears from glasses; from clothing such as hooks and eyes on brassieres and dresses, metal clips on brassieres and slip straps, garter buckles and corset stays. Other cutaneous areas of metal dermatitis may be less apparent. The chest, upper back or flank may be affected by zippers in clothing. The dress might be worn occasionally which adds to the obscurity of the contact. A recalcitrant dermatitis on the penis was traced to zippers in trousers. A patch of so-called neurodermatitis on the thigh, leg or forearm has been found to be due to contact with chrome furniture. Metal eyelets in shoes have been the cause of a dermatitis pedis. Hair pins must always be suspected in a scalp or neck dermatitis. The hand is a favorite site from carrying or holding metal objects. Waldbott[10] has published, in his monograph on contact dermatitis, excellent photographs illustrating the patterns of dermatitis on the hands produced by a wide variey of metal objects. Metal contact dermatitis tends to be more common in hot weather. A number of patients have noted that they can wear a wrist watch in cool weather without trouble, but in hot weather it produces a dermatitis. Wetness of the skin from perspiration is a predisposing factor.

The importance of metal as a source of contact dermatitis would bear a direct relationship to its possible incidence. An effort has been made to determine this by the following procedure. Pieces of various metals about dime-size were obtained from a jeweler and an electroplating company. They were kept in compartments of a plastic ice cube tray. The tests were done by placing the metal discs on a strip of Elastoplast in the same order that they were kept in the tray. The strip of tape was then placed on the subject's back, and the tests were read after forty-eight hours. This method permitted rapid testing and required the minimum of office time. Only patients with hand eczema were tested because these cases were the most plentiful, and the hands sustain an extensive exposure to metals.

The incidence found, appearing in Table I, was about 11 per cent for this group of cases. It was much higher in female patients, 10 per cent compared to 1 per cent in male patients. Irritative reactions were not recorded. These showed slight erythema which usually faded within one day. Two cases of chrome eczema were found in the series. Patient C.W.—a dentist, contracted the chrome dermatitis from holding chrome-plated instruments, and Patient J.D., from resting his hand on chrome

TABLE I. PATCH TEST INCIDENCE OF METAL SENSITIVITY IN SIXTY-EIGHT CASES OF HAND ECZEMA

	Male—19 Cases	Female—49 Cases						
Cases	D.W.	G.B.	J.F.	A.W.	A.R.	L.W.	J.D.	S.B.
Chrome (pure)	****	**	—	—			****	
Nickel (pure)	—	****	****	—			****	****
Silver coin ag 90% cu 10%	—	****	—	—		****		
Gold au 58% ag 30% cu 12%	—	**	—	**				
Copper (pure)	—	****	—	—				
Brass cu, zn, sn, pb, mn.	—	**	—	****	****			
Aluminum foil ?	—	****	—	—				
Stainless steel ni, fe, c, cr.	—	—	—	—				
Per cent	1%	10%						

Positive patch tests from various metals were noteworthy for the long duration of the reactions. Commonly, the site remained erythematous for a month or longer. Persistence or chronicity of the dermatitis is an important feature of a metal sensitization.

furniture. Many patients displayed "spot reactions" at points on the periphery of the discs. This was especially true in using nickel discs. It was felt that these resulted from tiny sharp points or minute fractures at the borders. Minute mechanical and metal irritations were thus produced. A sidelight to this observation is the frequency of irritative lesions on the fingers adjacent to the ring finger. Stones, setting metal for the stones and carvings on rings usually display sharp and fracture points which can easily injure the ring finger or the adjacent ones. People often adjust rings to the correct position with the adjacent fingers. This source of trivial injury often produces the onset lesion for the eventual development of hand eczema.[3]

The subjects showing positive tests usually displayed severe reactions. Flare-type responses developed in three cases. The reaction time was short, less than twenty-four hours in three subjects. In two patients it was only two hours. One subject noticed an exacerbation at a positive test site months later when the area was exposed to sunlight. This incurred speculation relative to photosensitization in some subjects sensitized to metal. In this case it was gold. Metal sensitivity had existed in one case ten years, and in another five years with no diminution in sensitivity.

While the incidence of metal sensitivity was being determined, a patient was seen with an acute dermatitis affecting the hands and forearms. It developed after being exposed to chromic acid crystals for several weeks. A patch test was performed with a 0.5 per cent aqueous solution of chromic acid.[9] Within a matter of hours a weeping patch of dermatitis covered the entire upper arm. The insurance company, the referring physician, the patient, and the author were most distressed by this unforeseen reaction. One case does not make an issue, but it would seem that the

TABLE II. DEGREE AND RANGE OF SENSITIVITY TO CHROMIUM

Chromium Compounds Tested*	Formula	Color	Solubility	Concentration Patch Tested	Reaction Time	Degree	Duration Time
Sodium chromate	Na_2CrO_4	yellow	sol.	1:200 aq.	5 hours	vesicles with flaring	subsided in 1 mo.
				1:20000 aq.	0	0	0
Potassium chromate	K_2CrO_4	yellow	sol.	1:10000 aq.	0	0	0
Chromic acid	H_2CrO_4	yellow	sol.	1:5000 aq.	72 hours	papules	5 days
				1:20000 aq.	0	0	0
Chromic oxide	Cr_2O_3	green	insol.	1:200 pt.	0	0	0
Chromic sulfate	$Cr_2(SO_4)_3$	blue	insol.	1:200 pt.	0	0	0
Zinc chromate	$ZnCrO_4$	yellow	insol.	1:200 pt.	72 hours	faint redness	1 day
Lead chromate	$PbCrO_4$	red	insol.	1:200 pt.	0	0	0

*Patch tests with metals: chrome, nickel, silver, tin, zinc, copper, brass, produced negative results. Aqueous solubility of chrome compounds is a determining factor for patch test reactions in subjects sensitive to chromium.

recommended concentrations for patch testing soluble chromium compounds are too strong. Shortly after this experience, a second patient was referred for treatment. Testing was carried out with extreme caution and only when the acute phase of the eruption had subsided.

CASE REPORT

Case 1.—C.B., a white man aged thirty-four, was examined for a dermatitis affecting the hands, forearms, face, neck, abdomen and dorsal feet. The first signs of the eruption had developed six weeks previously. It started in and around a scratch on the right fifth finger. Gradual spreading took place. The face, neck, abdomen and feet had been affected for only two weeks. This man was a welder of machine parts; these were washed in a 0.5 per cent aqueous sodium chromate solution. The parts were wet with the solution at the time of welding. He had been doing this type of work for a period of six months. Only after a trivial scratch had been repeatedly contaminated with chrome solution did the sensitization develop.[4] On the medial aspect of the right third finger was an ulcer, three millimeters in diameter. He thought this had appeared subsequent to the dermatitis on the fifth finger. The nasal septum was normal. A systemic review revealed no current or past illnesses. He had worked at farming, cab driving, and had done considerable painting during summers. The eruption involuted in the reverse manner to its spread; that is, the most recent areas healed first. The right fifth finger and flexor surfaces of the forearms developed lichenification before healing. The ulcer healed along with the resolution of the lichenification. The healing time was ten weeks. As soon as the diagnosis was made he was removed from contact with chromate. A month later a patch test was done with the original sodium chromate solution, concentration 0.5 per cent. Only one corner of the filter paper square was moistened with the solution. Again, a flare-type reaction was noted to this concentration. The patch test reaction did not produce any exacerbation in healed sites of dermatitis.

DISCUSSION

The chief concern of the patient with chrome dermatitis was to avoid a recurrence. The author was not aware of any studies dealing with the range of sensitivity to various chrome compounds. In order to obtain information that might prevent future recurrences, tests were carried out as shown in Table II. Three of the insoluble chrome compounds were tested

on the left arm, a site of previous dermatitis from patch testing to sodium chromate. The degree of sensitivity to soluble chrome compounds was found to rest between 1:5,000 and 1:20,000. This is much lower than that found for an organomercurial like merthiolate.[6] It would seem that patch tests with soluble chrome compounds would be safer if dilutions of 0.1 per cent, or better still 0.05 per cent concentrations were used. The latter is adequate for detection of chrome sensitivity.

Edmundson[1] patch tested fifty-six workers with chrome ulceration of the skin and/or nasal septum to a 0.5 per cent solution of potassium chromate. No evidence was found that these sequela, healed or active, predisposed to chrome sensitization. The history in Case 1, (C.B.), pointed to a trivial scratch at the site of the development of the chrome sensitization. Examination of this area revealed a faint line of erythema about 5 millimeters long with no inflammatory border, and palpation disclosed no induration. The chrome ulcer, however, showed a typical indurated border. It developed at a site of interdigital skin, known to be thin, whereas the sensitization developed on dorsal skin. This brings up the relation of the depth of action in the skin of chemical allergens that induce sensitizations. Are chemical allergens acting deep in the skin walled off by a prompt defensive tissue reaction? A good example is the border of a chrome ulcer. In chemical allergens acting superficially, as in scratches, the defensive tissue reaction is tardy, time accrues for the formation of sensitizing conjugates—the incubation period for sensitization—and what is more, the lack of a defensive tissue wall about the injury allows the sensitized linkages to spread. Sensitization dermatitis has been seen to develop so commonly in trivial injuries, especially when they are daubed with topical medicines, that several reports on this subject have been published.[1,2,4,6]

Jaeger and Pelloni[7] patch tested thirty-two patients with cement eczema and 168 patients with eczema from other causes with a 0.5 per cent solution of potassium bichromate. A positive test to chromate in thirty of the cases with cement eczema, allowed them to conclude that chromium salt was the actual cause. Was their testing solution too strong? The degree of sensitivity in their cases ranged up to 0.01 per cent for solutions of chromic acid and potassium bichromate. Rostenberg and Perkins[8] found no evidence of cross-sensitization between soluble chromium compounds in a patient sensitive to nickel and cobalt. The degree of sensitivity for cobalt was 1:10,000 and nickel only 1:200. A weak reaction to auric chloride (aqueous 2 per cent) was considered an independent sensitization. A patient sensitive to aged silver nitrate showed only an irritative reaction to silver foil.[5] Apparently, a positive reaction to aqueous solutions of various metals is not an indication that the metal itself will cause a dermatitis.

SUMMARY

In a series of sixty-eight cases of hand eczema, sensitivity to chrome metal was found in only two cases, an incidence of 3 per cent. The total

incidence of sensitization to various metals reached 11 per cent; much higher in the female patient, 10 per cent compared to 1 per cent for male patients. Nickel showed the highest ratio of four plus reactions. The solubility of chromium compounds was a determinate factor in producing positive reactions. A patient sensitive to soluble chrome compounds need show no reaction to the insoluble compounds or the metal itself. To avoid severe patch test reactions to soluble chrome compounds, it is recommended that higher dilutions be used, 0.1 or even 0.05 per cent. Workers exposed to soluble chrome compounds should be instructed to watch closely for any areas on their hands of onset eczematizations. Prompt recognition of their etiology would prevent much disability, even hospitalization, would reduce insurance costs, and most important, possibly prevent the development of sensitization to chromium. Jewelry customs of the women might be the explanation for the 10 to 1 sex-ratio of metal sensitivity. Onset lesions in eczema of the hands in females commonly appear under or adjacent to rings. Metal sensitivity is one facet of the problem of hand eczema.

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On December 1, one of our Sustaining Members, Center Laboratories, Inc., moved to their new address, 16 Sintsink Drive East, Port Washington, New York, where the laboratories are established in new and larger quarters with expanded facilities.

FAILURE OF A TYROSINE-NIACINAMIDE-PYRIDOXINE MIXTURE TO INFLUENCE ALLERGIC DISEASE

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AMONG THEORIES advanced to explain the allergic state and its symptoms is that of "histamine-epinephrine imbalance." According to this concept,[7] the allergic individual does not produce enough epinephrine to counteract the histamine or histamine-like substance released by the union of allergen and allergic antibody. If this be the case, it is necessary only to increase epinephrine production to redress the imbalance and relieve symptoms.

To provide the extra available epinephrine, Widmann and Keye have recently advocated the feeding of l-tyrosine to allergic patients.[7] According to the theory presented, l-tyrosine is a possible epinephrine precursor, and by flooding the body with this material epinephrine synthesis is increased. Niacinamide and pyridoxine are to be given with the tyrosine, to aid in the synthesis. These authors reported 60 per cent to 100 per cent improvement in 412 allergic patients to whom they gave daily doses of 4 to 36 tablets of the following mixture:

l-tyrosine	200 mg.
niacinamide	10 mg.
pyridoxine	2.5 mg.

Since this theory differs from our established ideas about the allergic reaction, and since a tablet of the above composition is available commercially (hereafter referred to as the "drug"), it seemed desirable to run controlled animal and clinical studies to test the theory, as well as to check the results of Widmann and Keye. Accordingly, two studies were set up: one on guinea pigs, to measure chronic toxicity and protection against histamine shock; the other on patients with chronic allergic disease, predominantly asthma, to compare clinical improvement on the drug and on a placebo.

Part I. Guinea Pig Studies

If the mixture containing tyrosine increases epinephrine production, which in turn counterbalances histamine, then animals adequately treated with the drug should be able to withstand histamine shock better than untreated animals.

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Presented before the Section on Allergy at the 82nd Annual Session of the California Medical Association, Los Angeles, May 24-28, 1953.

Dr. MacLaren is an Associate Fellow of the American College of Allergists.

TABLE I.

Group	Number Animals	Treatment with Drug	Histamine Diphosphate Dose	Survived	Total Percent Survived
1	10	None	0.4 mg./kilo	0/10	0 %
2	10	None	0.4 mg./kilo	3/10	33.3%
3	10	40 mg./kilo daily for 14 days	0.4 mg./kilo	3/10	33.3%
4	10	200 mg./kilo daily for 14 days	0.4 mg./kilo	3/10	33.3%

METHODS AND MATERIALS

Guinea pigs weighing between 250 and 350 grams were selected and divided into four groups.

Group 1. Determination of LD 100 of Histamine.—LD 100 is defined as that dose of a drug which is just lethal to 100 per cent of the test animals. Following the work of Fineberg et al, guinea pigs were given 0.3 mg of histamine diphosphate intracardially. This had to be increased to 0.4 mg per kilo of histamine phosphate before ten successive animals succumbed. Hence the figure of 0.4 mg per kilo was taken as the LD 100 of intracardiac histamine diphosphate.

Group 2. Controls.—These ten animals were not given anything other than their usual rations for two weeks during which the remaining groups were being fed the drug. On the fifteenth day they were injected intracardially with histamine phosphate 0.4 mg per kilo. Three survived.

Group 3. Normal Dose of Drug.—Ten animals were fed 40 mg per kilo of the drug daily for fourteen days. The drug suspension was given by stomach tube, which insured exact intake. This dose of the drug corresponds to 2,600 mg or 12 tablets daily for a 65 kilo adult person. On the fifteenth day these animals were injected intracardially with histamine base 0.4 mg per kilo. Three survived.

Group 4. High Dose of Drug.—Ten animals were fed by stomach tube 200 mg per kilo of the drug daily for fourteen days. This dose corresponds to 13,000 mg or 62 tablets daily for a 65 kilo adult person. On the fifteenth day, these animals were injected intracardially with histamine base 0.4 mg per kilo. Three survived.

Toxicity Test.—Five guinea pigs were fed the same dose of the drug as Group 4, but for three weeks. At the end of this time these animals, and one control, were killed and evidence of toxicity searched for at autopsy.

RESULTS AND COMMENT

The results of the histamine protection study are summarized in Table I.

Except for Group 1, in which an attempt was made to determine LD 100 for histamine base, the same percentage of animals succumbed in the treated and control groups. However, the figures for survival indicate that tyrosine-niacinamide-pyridoxine mixtures do not exert any protective action against histamine poisoning in guinea pigs.

None of the animals autopsied for signs of toxicity showed any gross pathologic changes. During treatment no ill effects were observed in any of the animals. It may be concluded therefore that this mixture is nontoxic to guinea pigs in the doses used.

Part II. Clinical Studies

MATERIALS AND METHODS

Through the kindness of the Stuart Company of Pasadena, and the International Minerals and Chemical Corporation of Chicago, the Allergy Clinic of the Los Angeles County Hospital was supplied with tablets con-

taining l-tyrosine, niacinamide and pyridoxine in the proportions given, as well as a placebo of identical appearance. The drug and the placebo were coded and their respective identities unknown to the investigators until the present series was completed.

Twenty-one adult, and thirteen child patients, were chosen at random from the Allergy Clinic clientele. The features of this group are shown in Table II.

TABLE II.

Features	Number
Sex	
Male patients	10
Female patients	24
Diagnosis	
Asthma	27
Hay fever and asthma	8
Hay fever only	4
Allergic cough	5
Chronic vasomotor rhinitis	4
Chronic urticaria	1
Age Range—years	
Adults	32-63
Children	3-14
Asthmatic Adults	
Below age 45	11
Above age 45	10

No patients were included who were obviously improving on regular treatment. The majority of these patients had been desensitized for many months and were getting maintenance doses of vaccine. These doses were not changed during the six-week period of study. All but five patients were taking some form of palliative treatment, such as aminophylline, antihistamines, "asthma pills" (containing theophylline, ephedrine and phenobarbital), iodides, nose drops or epinephrine by injection or nebulizer. These medicines were being taken only as needed, and the amount used closely paralleled the severity of symptoms.

The children were given two tablets of the drug, or placebo, three times a day; the adults two tablets four times a day. These doses were chosen for two reasons. First, it was found that large doses of sixteen or more tablets daily, caused nausea, sweating and dizziness in many patients. Second, we wanted to keep the dosage in the range comparable to standard drug usage. Half the patients were given the drug for the first three weeks, then changed to the placebo for the second three weeks. The other half of the group got placebo first, followed by the drug. A deliberate attempt was made to present the new tablets in as neutral a manner as possible, so as to avoid improvement by suggestion.

Each patient kept a daily record of symptoms, of palliative medication used, and such associated events as colds or unusual exposure to allergens. At each weekly visit he was questioned carefully to make sure his records were reliable.

Improvement, or lack of it, was judged simply by counting the number of attacks of symptoms, the amount of medication used in one three-week

TABLE III.

Patient	K.R.	M.N.	R.S.	H.E.
Age Sex Diagnosis	33 F Asthma	34 F Hayfever	14 F Asthma	47 M Asthma
Symptom Units*				
1. On drug 2. On placebo	26 54	67 34	38 35	48 50
Medication Units*				
1. On drug 2. On placebo	72 104	94 44	13 14	13 16
Symptoms better on— Medication less on—	drug drug	placebo placebo	no change† no change	no change† drug

*Total for 3 week period.
†Less than 10 per cent difference.

TABLE IV.

	Symptoms			Medication		
	Adult	Child	Total	Adult	Child	Total
Patients better on drug	8	4	12	6	3	9
Patients showing no change*	4	7	11	4	4	8
Patients better on placebo	9	2	11	9	3	12
	21	13	34	19	10	29†

*Less than 10 per cent difference between drug and placebo.
†Five patients were taking no palliative medication and so are not included in this total figure.

period, and comparing this with the other three-week period. If a patient were taking aminophylline tablets and using epinephrine, each tablet and each use of epinephrine was counted as a medication "unit." Similarly each attack of wheezing, of hives, or sneezing was counted as a symptom "unit."

RESULTS

To illustrate, this method of recording results the data on four typical patients are given in Table III.

Table IV summarizes the results on thirty-four patients, giving the number of adults and children that did better on either the drug or the placebo, or who showed no change (less than 10 per cent difference).

Of the twenty-seven patients with asthma, twelve did better in regard to symptoms and medication on the drug, eleven did better on the placebo and four showed no change.

The four patients with simple hay fever make up too small a group from which to draw conclusions, but two did better on placebo, one on the drug and one showed no change. The one patient with chronic urticaria recorded forty-eight attacks in three weeks on drug, and fifty-eight attacks on placebo.

Analysis of these patients failed to show any correlation between improvement (or lack of it) on the drug, and such things as age, duration of symptoms, type of allergic disease, or presence of skin sensitizing antibodies.

A group of fifteen private patients was also given the tyrosine-niacinamide-pyridoxine mixture by one of us (B.C.E.). In this group there were seven children and eight adults. The chief complaint was asthma in eight, eczema or neurodermatitis in five, and hay fever, angioedema and migraine, each in one case.

The drug was given in daily doses of 400 to 600 mg for two to six weeks. During this time all other medication was omitted. No placebo controls were used. None of these patients showed any change for the better.

SIDE REACTIONS

Seven of the clinic patients and two of the private patients, or 18 per cent of the total group, complained of undesirable reactions to the drug. These included flushing, sweating, nausea, faintness, or aggravation of symptoms, mainly asthma. Four patients discontinued treatment because of reactions.

COMMENT

This study failed to show any significant benefit to thirty-four allergic clinic patients and fifteen private allergic patients from the oral administration of a tyrosine-niacinamide-pyridoxine mixture. In the clinic group approximately as many patients (eleven) did better on a placebo as on the drug (twelve). Stated another way, one third of the patients did better on the drug, and two thirds showed either no change or did better on a placebo. By alternating drug and placebo, and by giving each for three weeks, any real curative effect should have become apparent. Thus this study did not substantiate the good results previously reported by others.

The negative results could be due to any or all of the following factors: (a) the theory that histamine-epinephrine imbalance is the cause of allergic symptoms is wrong; (b) l-tyrosine, while a possible precursor of epinephrine, is not necessarily used as such by the body; (c) extra epinephrine, even if produced by tyrosine, is not used by the body to combat chronic allergic states.

There are several objections to the histamine-epinephrine imbalance theory of allergic disease. The range of blood histamine in normal persons is approximately the same as in allergic patients.[3] Nor is there any evidence that the allergic individual cannot produce normal amounts of epinephrine in response to an adequate stimulus. Finally, recent studies[4,5,6] have shown that circulating histamine is actually raised after epinephrine injection. This observation has led to the successful use of antihistamines to counteract the untoward effects of epinephrine on the lung,[1,2] and in the treatment of "epinephrine fastness."[8]

Both the negative results in the guinea pig histamine-protection study and in our allergic patients tend to confirm points (b) and (c). The animals in particular, were given very large doses of the drug, and should

have shown striking resistance to histamine had they been well supplied with epinephrine. These results should be compared with the marked protection obtained with the usual antihistaminic drugs.

SUMMARY

1. Guinea pigs fed for two weeks on a mixture of l-tyrosine, niacinamide and pyridoxine were not significantly protected against histamine shock.

2. Thirty-four allergic patients were given 6 to 8 tablets daily of the following composition:

l-tyrosine 200 mg.
Niacinamide 10 mg.
Pyridoxine 2.5 mg.

3. Each patient was given the tyrosine mixture for three weeks and controlled three weeks by use of a placebo.

4. Improvement or lack of it, was measured by counting attacks of symptoms and amount of palliative medication taken during each three-week period.

5. Twelve patients fared better on the tyrosine mixture, eleven better on the placebo, and eleven showed no difference between the two.

6. Fifteen private patients with allergic disease showed no change in symptoms on the tyrosine mixture.

7. The tyrosine mixture appeared not to influence favorably these cases of chronic allergic disease.

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HYPOSENSITIZATION BY COMBINED ANTIGEN-CHLOR-TRIMETON INJECTION

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WHENEVER APPLICABLE, hyposensitization to specific allergens is the treatment of choice in the management of the allergic patient. The procedure has certain drawbacks in that systemic or local reactions occur particularly in highly sensitive individuals. In some instances these reactions result in discomfort to the patient; in others, the reaction may be serious and in some, inability to tolerate antigen may prevent satisfactory desensitization. Several investigators[1,2,3,4] have reported on the use of antihistamines orally or by injection as a method of decreasing reactions to antigen. Although results generally were satisfactory with injection, the rather large volume of solution required (1 to 2 cc) militated against the general use of these drugs. Sanger, et al,[4] and Jenkins[2] reported excellent results with Chlor-Trimeton 100 mg/cc in hyposensitization and treatment of allergic reactions. Simon[5] demonstrated its value in the prophylaxis of penicillin reactions.

The high concentration and high potency of Chlor-Trimeton make practicable the use of injectable antihistamine with antigens or other drugs, inasmuch as the average effective dose (5-10 mg) is contained in a volume of 0.05 cc to 0.1 cc.

METHOD

A series of 488 patients with various allergies, all of whom were receiving hyposensitization therapy, were treated by combining Chlor-Trimeton Maleate Injection* 100 mg/cc with the treatment antigen. The treatment antigen consisted of dust, molds, bacteria and mixtures of tree, grass and weed pollens according to the needs of the individual case. An attempt was made to give maximum pollen dosage, that is as high a dosage of pollen as could be tolerated without reaction, either local or systemic. The dose of Chlor-Trimeton ranged between 3 to 15 mg in adults, with 5 mg being the average dose. Twenty-four children (six to twelve years) were given 1 to 2 mg. The Chlor-Trimeton was withdrawn into the syringe containing the antigen, the solutions mixed by inverting the syringe, and given by subcutaneous injection.

RESULTS

In this entire series of 488 patients who received a total of 2,500 injections of antigen-Chlor-Trimeton mixture, there were only three instances of systemic reactions to antigen. Local reaction to antigen occurred

*Supplied by Schering Corporation, Division of Clinical Research, through the courtesy of George Babcock, Jr., M.D.

TABLE I. RESULTS OF THERAPY USING COMBINED CHLOR-TRIMETON-ANTIGEN INJECTION TECHNIQUE

Allergy	Total Number Cases	Percentage—Degree of Relief			
		Excellent	Good	Slight to None	Total Satisfactory
Hay fever	121	72	15	13	87
Perennial rhinitis	310	68	12	20	80
Atopic dermatitis	31	29	19	52	48
Asthma	26	—	15	85	15

in seventy cases or 14 per cent. In the group as a whole, excellent results were obtained in 307 cases or 63 per cent, good results in sixty-five cases or 13 per cent, making a total of 76 per cent satisfactory, and poor or no results in 116 cases or 24 per cent. Considering the variety and types of cases treated, this was considerably better than the results obtained in a group of 500 patients comprising the same types of cases treated before Chlor-Trimeton was combined with the antigen. In this former group excellent results were obtained in 55 per cent, good results in 12 per cent, or a total satisfactory of 67 per cent and poor results in 33 per cent. By being able to give increased pollen dosage, the total number of injections could be reduced in many of these patients. Table I summarizes the results of therapy in various groups.

Seasonal Hay Fever.—Among the 121 cases treated, 105 cases or 87 per cent obtained good to excellent relief of symptoms as a result of therapy. In practically all cases there was prompt (fifteen to thirty minutes) temporary improvement of symptoms which lasted from four to twenty-four hours, and occasionally longer. The combination of the antihistamine with the antigen, was especially helpful in patients reporting late for treatment, or in those not responding well to the usual therapy.

The dosage of the pollen antigen varied with each patient, but in general was increased .03 to .05 cc in the lower strengths (up to 1 per cent) and about .02 cc when using 3 per cent solution when given perennially and preseasonally. In most cases dosage was held stationary or increased very gradually during the pollen season. In at least half of the patients being treated with pollens, the lower strengths could be increased about .05 to .07 cc and the stronger solution could be increased about .03 cc. This resulted in about 50 per cent more pollen antigen being given in these cases. The frequency and total number of visits showed much individual variation but in general, the intervals of visits were changed from three to four weeks for those on perennial treatment schedules, and from once to twice a week up to one to two weeks of those on preseasonal treatment, making about a 20 per cent reduction in total visits. Those receiving seasonal treatment were usually seen once to twice a week in either instance, but those cases which received combined antigen Chlor-Trimeton treatment seemed to obtain more relief. There were two systemic reactions (con-

sisting of asthmatic attacks relieved by epinephrine) in the group during the entire treatment period.

Perennial Vasomotor Rhinitis.—The 310 cases comprised the largest group treated. The results were gratifying, with 248 cases or 80 per cent obtaining good to excellent relief. As with the hay fever patients, there was a prompt (fifteen to thirty minutes) improvement of symptoms which lasted from three hours up to one or two days in most instances. The antigens employed were usually dust, molds, and bacteria, plus pollens in those cases with seasonal exacerbations. As a rule it was not usually possible or necessary to increase the dosage of the non pollen antigens above that customarily employed before combined antigen Chlor-Trimeton treatment was instituted. The average dose of Chlor-Trimeton was 5 mg. There was only one case in which a systemic (asthmatic) reaction to the antigen occurred.

Atopic Dermatitis.—The thirty-one cases treated were thought to be sensitive to dust and this antigen was combined with the Chlor-Trimeton. In nine cases or 29 per cent the pruritus was considerably relieved and the skin condition cleared more rapidly than usual. In another six cases or 19 per cent there was moderate control of pruritus. The remaining 52 per cent showed very little or no improvement of pruritus immediately following injections. The average dose was 10 mg by subcutaneous injection.

Asthma.—Only four out of twenty-six cases of asthma obtained temporary improvement of symptoms with injections of Chlor-Trimeton, and consequently its use was continued only in these patients and a few who had persistent local reactions to antigen. In these patients 5 mg was the usual dose.

SIDE EFFECTS

There were very few side reactions to Chlor-Trimeton Injection 100 mg/cc in this series. Drowsiness was infrequently encountered, being present in thirty-six patients or 7 per cent. In no case was this severe and when it occurred, it was generally in those patients receiving relatively large doses of the drug. Nervousness, nausea and dry mouth were only rarely noted. No patient had severe reactions to this drug. A few patients complained of transient pain or burning lasting for a few seconds at the injection site.

CONCLUSIONS

1. The injection of Chlor-Trimeton 100 mg/cc along with the appropriate treatment antigen offers these advantages.

(a) The incidence and severity of local and systemic reaction to antigens is markedly lessened.

(b) Higher doses of antigen are well tolerated by patients in whom it is desired to increase the dosage.

(c) Prompt temporary relief of symptoms lasting from four to twenty-four hours usually occurs as a result of antihistamine therapy.

2. Chlor-Trimeton Injection is well tolerated locally and systemically. No severe reactions were noted.

SUMMARY

A group of 488 patients with various allergies has been treated by combining Chlor-Trimeton Maleate 100 mg/cc with treatment antigens. The results were considered extremely beneficial in that both local and systemic reactions were lessened, the doses of antigens could be considerably increased, and the patients were usually given immediate temporary improvement of their symptoms. This combination of treatment is considered so useful that it is believed it will, in the future, be considered part of standard treatment practice in many allergies.

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CARBOMYCIN THERAPY

Results with carbomycin in treatment of 31 patients with pneumococcal pneumonia were decidedly inferior to those obtained with other antibacterial agents. Blood and urine concentrations of carbomycin following oral administration were irregular and usually insufficient to inhibit common pathogens. This was true even though carbomycin was administered in maximum tolerated dosage. It is concluded that this new antibiotic can not be recommended in treatment of bacterial infections and is specifically contraindicated in treatment of pneumococcal infections.—Finland, M., et al., New England J. M., 249:310, 1953.

EVALUATION OF A NATURAL STEROID COMPLEX (MARISONE) IN THE TREATMENT OF ALLERGIC DISORDERS

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THE INTRODUCTION of corticotropin and cortisone in the treatment of rheumatoid arthritis, and the subsequent demonstration of their beneficial effects in bronchial asthma and other allergic disorders,[1,3,5,8,13] has instigated the search for substitute substances which would have the same beneficial effects in these various conditions, yet be less expensive and provoke less troublesome and severe side reactions. Many substances have been tried and found to be relatively ineffective, among them being the combination of desoxycorticosterone acetate with large doses of ascorbic acid by injection,[2,9,10,12] and pregnenolone.[4,6,10]

In 1951, Jaros and Spielman[7] reported on a natural steroid complex (Marisone), derived from pregnant mare's urine, from which the estrogen conjugates had been removed. They reported that certain actions of Marisone, especially its effect on peripheral eosinophilia, resemble those produced by some of the adrenal corticoids. This steroid complex was administered orally to fourteen patients with severe intractable asthma. All patients showed subjective improvement within the first week of treatment, with improvement of vital capacities coming on more slowly. Continued medication did not prevent the recurrence of subsequent asthmatic episodes. These symptoms, however, were less severe than in the original attacks. The authors concluded that Marisone was of benefit in the treatment of bronchial asthma and that its effect was similar to that of corticotropin and cortisone but on a much lesser scale.

In a subsequent study Spielman and Blau[11] showed that Marisone was beneficial in the treatment of atopic dermatitis and chronic urticaria, the first sign of improvement being a cessation of pruritus, followed subsequently by a regression of the skin lesions.

Because of these favorable reports, it was decided to study the effects of Marisone on various cases of respiratory allergy.

PROCEDURE

Marisone* was supplied in capsules of 200 mg each. There were three categories of cases treated: ragweed hay fever, perennial allergic rhinitis and bronchial asthma. Patients were given 600 mg daily, in three divided doses, and if there was no improvement after one week the dose was increased to 1200 mg daily, in three divided doses. Most of the patients were

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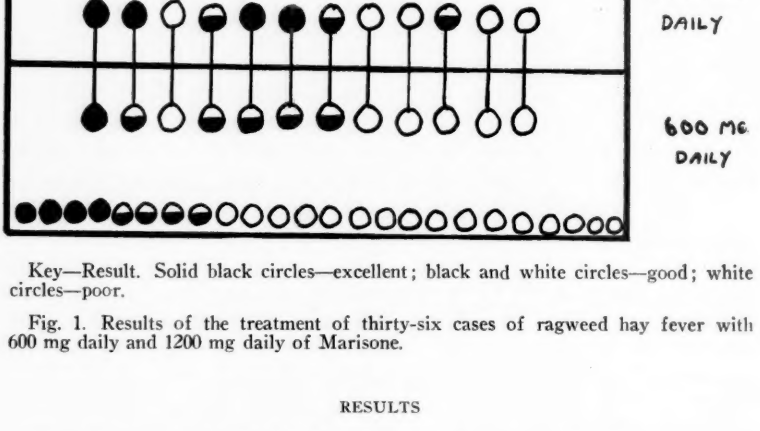
*Marisone was supplied through the courtesy of Ayerst, McKenna and Harrison, Ltd. of New York.

also given placebo capsules of the same color and design, to be taken at the same intervals. Placebos were administered for the first week and then, if no change in symptoms occurred, Marisone therapy as outlined was instituted thereafter.



Key—Result. Solid black circles—excellent; black and white circles—good; white circles—poor.

Fig. 1. Results of the treatment of thirty-six cases of ragweed hay fever with 600 mg daily and 1200 mg daily of Marisone.

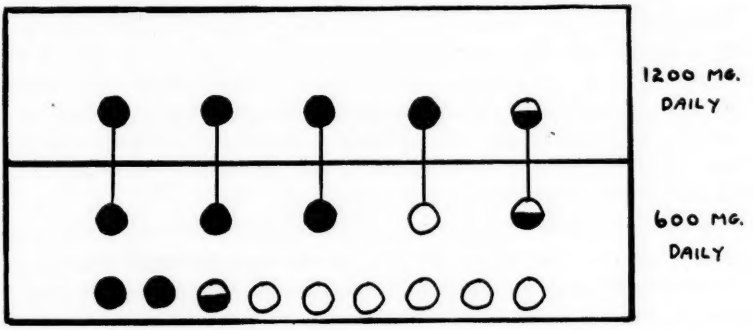
RESULTS

Hay Fever.—A total of thirty-six cases was treated. Of this group eight, or 22 per cent, had excellent results (90-100 per cent relief of symptoms); seven, or 19 per cent, had good results (at least 50 per cent relief of symptoms); and twenty-one, or 59 per cent, had little or no relief of symptoms. Combining the excellent and good results we find that fifteen, or 41 per cent, of the hay fever patients showed definite amelioration of symptoms with the Marisone therapy. Figure 1 depicts these results graphically. It will be noted that some patients who did poorly on 600 mg daily, fared better when the dose was increased to 1200 mg daily. In only an occasional case did the placebo therapy yield beneficial results and, in such cases, the Marisone therapy was not used.

Perennial Allergic Rhinitis.—A total of fourteen cases was treated. Six, or 43 per cent, had excellent results; two, or 14 per cent, had good results; and six, or 43 per cent, had no results. Again, combining the excellent and good results, we note that Marisone had a definite beneficial effect in eight, or 57 per cent, of the cases. In this group in particular, the most beneficial results were noted in the alleviation of nasal blocking. These results are illustrated in Figure 2.

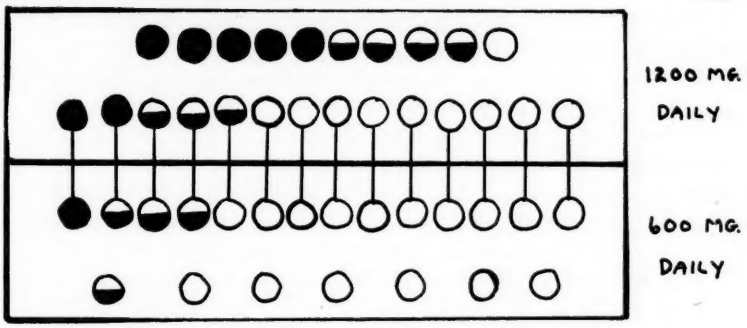
Bronchial Asthma.—A total of thirty-one cases was treated. Seven, or 22 per cent, had excellent results; eight, or 26 per cent, had good results;

and in sixteen, or 52 per cent, the results were poor. Combining the first two groups we observe that Marisone was of definite benefit in fifteen cases, or 48 per cent of the total. These results are illustrated in Figure 3.



Key—Result. Solid circles—excellent; black and white circles—good; white circles —poor.

Fig. 2. Results of treatment of fourteen cases of perennial allergic rhinitis with 600 mg daily and 1200 mg daily of Marisone.



Key—Result. Solid circles—excellent; black and white circles—good; white circles —poor.

Fig. 3. Results of treatment of thirty-one cases of bronchial asthma with 600 mg daily and 1200 mg daily of Marisone.

SIDE REACTIONS

Side reactions were noted in twenty-two patients. These consisted of dizziness, headache, nausea, abdominal cramps, urticaria, flushes, joint pains, drowsiness, belching and indigestion. Generally, one side effect was noted for each patient, but in six cases there were combinations of side effects, such as dizziness with headache, headache with nausea, or nausea with belching and indigestion. In most cases side effects were mild and wore off with persistence of medication. In five cases, however, symp-

toms were of sufficient severity to force discontinuance of medication after one to two days.

DISCUSSION

Evaluation of the effects of any new drug in allergic disease is always beset by pitfalls, since allergic conditions are frequently, if not always, characterized by spontaneous remissions and exacerbations. In addition to this, our series of cases is admittedly small, totalling eighty-one cases in all. Nevertheless, some comparisons and inferences can be drawn from our data, especially when evaluated in the light of the many reports of the results obtained with the cortical steroids.

There is no doubt that cortisone and corticotropin are very potent therapeutic agents, a fact which is borne out by the many reports in the literature. Marisone, on the other hand, is much less potent, less dangerous to use, and results in less troublesome side effects. Beneficial effects of Marisone in about 50 per cent of the patients in this study suggest further investigation in larger groups of patients. Such studies may lead to the development of other similar but more effective therapeutic agents.

It may be of some interest to comment in detail on some of the effects noticed with Marisone. In nasal allergy, both seasonal and perennial, the outstanding effect of Marisone was the relief of nasal blocking with little relief of sneezing or rhinorrhea. Dramatic results were obtained promptly in two cases of hay fever. In bronchial asthma there was relief of bronchospasm, in some cases rapidly and in others more slowly and only after increased dosage. Easier expectoration was also noted. In four cases of intractable asthma, Marisone gave such prompt and prolonged relief that plans to resort to cortisone therapy were abandoned. In most cases, however, the improvement did not persist in spite of continued medication. Also, there was no protection against recurrent attacks or exacerbations of asthma, findings consistent with those of Jaros and Spielman.[7] In general, the beneficial effects of Marisone were most apparent in bronchial asthma, less striking in perennial allergic rhinitis and least in hay fever, although dramatic results were obtained promptly in two cases.

SUMMARY

1. A total of eighty-one cases with allergic disorders were treated orally with a natural steroid complex known as Marisone, derived from pregnant mare's urine. The total dose was 600 to 1200 mg daily in divided doses.

2. The cases under study included seasonal rhinitis, perennial rhinitis and bronchial asthma. Of thirty-six cases of hay fever, fifteen (41 per per cent) yielded satisfactory results. Of fourteen cases of perennial allergic rhinitis, eight (57 per cent) gave satisfactory results. Of thirty-one cases of bronchial asthma, fifteen (48 per cent) yielded satisfactory

results. The outstanding effects of Marisone therapy were the relief of nasal blocking in the nasal allergy cases, and the relief of bronchial spasm in the asthmatic cases.

3. In most cases relief of symptoms was not persistent, in spite of continued medication and increased dosage; this was especially true among the asthmatics, in whom exacerbations of asthma, although milder, were not prevented by Marisone.

4. In 27 per cent of the patients under therapy, side reactions, usually mild, were noted. These effects included dizziness, headache, nausea, abdominal cramps, urticaria, flushes, joint pains, drowsiness, belching and indigestion. In five patients the side effects were sufficiently severe to necessitate a discontinuance of therapy after one to two days.

5. In the treatment of respiratory allergy, Marisone proved effective in about one-half of the cases treated, affording good but temporary symptomatic relief. It is definitely less potent and less effective in such cases than corticotropin or cortisone. The therapy was most effective in bronchial asthma, less effective in perennial allergic rhinitis and least effective in seasonal hay fever.

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9538 Kingshighway (Dr. Bloom)

Case Reports

SENSITIVITY TO INTRAVENOUS PROCAINE

Three Case Reports

FRED F. DeBOLD, M.D. AND LOUVANE A. FOX, M.D.
Keene, New Hampshire

AFTER HAVING successfully relieved acute traumatic sprains and other injuries, Graubard and Peterson[4] (in 1947) began to use intravenous procaine for the symptomatic treatment of arthritis. Procaine, they discovered, was concentrated seven or eight times more at the site of injured tissue than in other parts of the body. They also learned that procaine is rapidly broken down in the body and that twenty minutes after rapid intravenous injection no trace of it can be found in the blood stream. Therefore they proposed the so-called "procaine unit:" 4 mg of procaine per kilogram of body weight to be administered in twenty minutes. Their clinical experience showed that 0.1 per cent solution of procaine hydrochloride in isotonic saline solution could be tolerated by most all patients.

Sachs[6] reported in 1949 on a series of 2,000 adminisistrations of procaine in which there were no cases of sensitivity. Doud[3] reported in 1951 on eighty intravenous procaine anesthesias with no sensitivity reactions. Kerr and Brehm[5] reported in 1950 on 271 injections with no cases of sensitivity. Davis and Karp[2] reported in 1950 on 2,000 cases none of whom suffered reactions. On the other hand Criep and Riberio[1] list one death and two cases of anaphylactic reactions to procaine.

We began the use of intravenous procaine for the treatment of arthritis during the latter part of 1948, on patients who came to the clinic for this purpose. The technique we use is as follows: with the patient in a reclining position, the Abbott liter infusion solution of intravenous procaine (0.1 per cent) is used. The total dose for each patient is 4 cc of solution per kilogram of body weight injected through a 19-gauge needle. The flow of solution is started at twenty to thirty drops a minute and increased if no symptoms occur. If nausea or dizziness are experienced the intravenous rate is slowed for a short period of time. The total dose is given within twenty minutes, if possible. The patient should remain prone for about ten minutes following cessation of the treatment. Some patients had from ten to twenty treatments. Although originally we used intravenous procaine only for arthritis, later we similarly treated bursitis, myositis, pruritus, acute back pain, myalgia, sciatica, sprains, and some patients with idiopathic pain.

We now have given a total of over 1,600 intravenous procaine treatments to 300 patients. In this series there have been three reactions to procaine, no others having been found to be sensitive to the drug.

Case 1.—The first patient was a thirty-four-year-old man who had been admitted to the hospital for severe asthma. Very quickly following intravenous procaine injection he developed pain in the chest, much dyspnea, severe wheezing, and great apprehension. On questioning, it was discovered that he had a known sensitivity to procaine. Intravenous procaine was discontinued immediately. The patient had severe wheezing for fifteen minutes, responding well to aminophylline and epinephrine given intravenously.

Case 2.—The second patient, a forty-two-year-old housewife, suffered from acute back strain. There was no personal or family history of allergy. Shortly after initiating intravenous procaine the patient complained of nausea and shortness of breath. She then began to have a tremor involving the entire body. The rate of intravenous procaine injection was then slowed but the patient continued to have nausea and generalized tremor. The intravenous procaine was discontinued. The tremor lasted for about twenty minutes, during which time the pulse was 86, the blood pressure 112/60, and the temperature, 97° F. No aminophylline and epinephrine was used. She made a rapid recovery, and no further procaine therapy was ever given.

Case 3.—The third patient was a forty-eight-year-old white housewife who was being treated for a severe pruritus. There was no individual or family history of allergy. Shortly after beginning the intravenous procaine, the patient began to complain of severe shortness of breath. She then became very flushed; her respirations became very labored and moist, and her pulse, rapid. She had a total of about 100 cc of fluid intravenously before the treatment was discontinued. She was given epinephrine which gave her very little relief from the dyspnea, but it did stop her wheezing, and the flushing disappeared. The patient recovered in approximately an hour.

In summary, intravenous procaine was given to 300 patients with a total of over 1,600 injections. There were three reactions to procaine in this series.

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CONTACT DERMATITIS DUE TO THE CORD OF A HEARING AID

ALFRED J. WEIL, M.D., F.A.C.A.
Pearl River, New York

MODERN chemurgy complicates the determination of the sensitizing agent in contact dermatitis. The basic components of a suspected item must be considered, as well as admixtures, coloring matters or plasticizers; and dyes, varnishes, or lacquers.[1] An excellent monograph on contact dermatitis has just become available.[3]

The following account of a case is given because (1) it concerns a component of a frequently used gadget, on which no report on sensitizing has been found in the available literature; (2) it involves a plastic material, for which only few cases of sensitization have become known; and (3) it emphasizes the value of thorough examination. The patient, an old lady, had noticed only a lesion in the region of the ear, but a second and diagnostically decisive localization was discovered, when she disrobed.

Mrs. C.G., a seventy-six-year-old widow, was first seen on March 2, 1953. During the preceding week an itching and weeping skin affection had developed on and around her right ear. She had obtained new plastic frames for her eye glasses some time previously and she suspected this to be the source of difficulty. A hearing aid with a plastic ear piece had been used for several years. She had purchased a new cord for the hearing aid several weeks prior to the onset of her skin affection.

Objective Findings.—The skin of the right ear lobe, the adjoining area over the parotideal space, and behind the ear, was red, swollen, and excoriated in several places. Small vesicles were seen in the periphery of the involved areas. The denuded parts showed crusts and maceration. Over the middle of the clavicle a similar lesion was found. It was roughly about the size of a half dollar and was not excoriated. At this site the cord of the hearing aid was in close contact with the skin. Physical examination was otherwise negative except for hardening of the palpable arteries and a moderate elevation of the blood pressure (160/90 mm Hg.). Circumstances beyond our control prevented us from doing patch tests to confirm the clinical impression.

No local treatment was given other than calamine lotion. The cord was sheathed with close fitting tubing of pure latex rubber. Within two days the affection improved and completely disappeared in ten days. The patient reported by letter at the end of March that there had been no recurrence.

The hearing aid is of a nationally known make, but the inculpated cord was not the original one. It had been purchased from an unknown source, and the flesh-colored plastic covering was made of a vinylite type material. The original cord was used without trouble after it had been repaired.

Sensitization to the plastic portion of hearing aids has been observed[3] but reactions due to the cord were not found recorded in the available literature. Vinylite type plastics have been reported as agents of sensitization in a few cases.

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Editorial

The opinions expressed by the writers of editorials in the ANNALS *do not necessarily represent the group opinion of the Board or of the College.*

ACUTE ANAPHYLACTOID REACTIONS ATTRIBUTABLE TO PENICILLIN

Under this title, *Antibiotics and Chemotherapy* published in its September, 1953 issue (page 891) a survey by H. Welch and co-workers (U. S. Food and Drug Administration) covering a number of metropolitan hospitals with a total of 51,000 beds (approximately 6 per cent of the total bed capacity of general hospitals in this country). Information on not less than sixty-three cases of severe anaphylactoid shock was obtained, including nineteen fatalities. Four reactions could be attributed to streptomycin (three of these after intrathecal injection). The rest was due to penicillin, with eighteen fatalities, two of which occurred after injection of penicillin O. In only one case had the agent been administered by the oral route.

The survey disclosed no anaphylactoid reaction attributable to any of the other antibiotics, particularly chloramphenicol, aureomycin, and terramycin. The question is raised, whether the absence of such experiences is due to the fact that these antibiotics are administered largely by the oral route.

In addition, twenty-five anaphylactoid reactions with five deaths were reported following the administration of penethamate (Neo-Penil), some of which possibly might have been due to toxicity rather than allergic reaction.

What is of particular impact for the allergist is the fact that among the eighty-eight patients, twelve had previous evidence of sensitivity and not less than twenty-six had a history of asthma, hay fever or other allergies. The increased risk of persons "stigmatized" to develop allergic reactivity has been stressed repeatedly in previous discussions of the problem of serious accidents after drug administration. But none of the data known to this writer gave such convincing evidence concerning this point of paramount importance to our specialty.

A.J.W.

In Memoriam

FRANK G. CRANDALL

Frank G. Crandall was born in Omaha, Nebraska, July 7, 1896. He received his medical degree from the University of Nebraska College of Medicine in Omaha in 1921, following pre-medical education at Central College, Fayette, Missouri. In 1916, he served on the Mexican border with the Missouri National Guard. He was a member of Phi Chi medical fraternity. He served his internship at Lord Lister Hospital in Omaha and practiced both in Iowa and Missouri before moving to Southern California in 1927. Doctor Crandall took postgraduate studies at Stanford University Medical School in 1939. He served as Assistant County Health Officer and Assistant City Health Officer of Los Angeles, and as Chief Epidemiologist, and for many years was Special Allergy Consultant. He was a reserve officer in the Army Medical Corps from 1923 until Pearl Harbor in 1941, at which time he was called to active duty and served as a Colonel in the Medical Corps until 1945. During this period, he was Medical Inspector at Camp San Luis Obispo; Commanding Officer of casual officers and enlisted men, San Francisco Port of Embarkation, South Pacific Convoy, 37th Division, Reinforced; Port Surgeon, First Port of Embarkation, Auckland, New Zealand; Medical Liaison Officer Headquarters Staff, Commander of South Pacific (Navy) and Headquarters U. S. Army South Pacific Area in the Guadalcanal and Solomon Islands Campaign. Colonel Crandall at this time became seriously ill, was hospitalized, and returned to the United States. Later he served as Commanding Officer of the Hospital and Camp Surgeon, Camp Abbot, Oregon. Following that, he was Executive Officer and Medical Director of Hammond General Hospital (Army) Modesto, California.

For many years, Doctor Crandall specialized in allergy and limited his practice to that specialty. In 1946, he published "It's An Allergy" which was recommended by the Book-of-the-Month Club in March, 1947. He was honored in 1947 by Central College, Fayette, Missouri, when he was awarded the Distinguished Alumnus Plaque at the commencement exercises. He was a member of the Executive Council of the Los Angeles County Medical Association, president of the Los Angeles Society of Allergy and the Pacific Coast Society of Allergy, having served as secretary of both organizations. He was consultant in allergy to the California, Hollywood Presbyterian, Orthopedic, French, and St. Joseph's Hospitals in Burbank, and attending physician on the Allergy Service of the Los Angeles County General Hospital. He was a lecturer in allergy to the interns, nurses and residents of a number of hospitals in the Los Angeles metropolitan area. In 1950, he was chairman of a Smog Committee for the Los Angeles County Medical Association. He was founder and secretary of the Southern California Chapter of the University of Nebraska College of Medicine Alumni Association, a member of the editorial board of *Annals of Western Medicine and Surgery*, Director of the Allergy Clinic of the Marion Davies Foundation for Children, and of the University of California Los Angeles Medical Department. He was a Fellow of the American Academy of Allergy and an Honorary Fellow of the American College of Allergists.

Doctor Crandall died August 25, 1953, in Los Angeles. He is survived by his widow, Mrs. Edith K. Crandall, two daughters, Mrs. Laura Crandall Robertson and Mrs. Eleanor Crandall Downs, and a sister, Mrs. Grace Crandall Richardson.

Officers and members of the College extend their sincere sympathy to the family and friends of our honored colleague.

IN MEMORIAM

HINTON D. JONEZ

It is with regret that we announce the recent death of Hinton D. Jonez, which occurred in Tacoma, Washington. Dr. Jonez was born in Knoxville, Tennessee, August 18, 1890. He attended high school in Seattle and received his medical degree in 1913 from the University of Oregon Medical School. He interned at Multnomah County Hospital, Portland, Oregon. Doctor Jonez acted as health officer of Pierce County, Washington, from 1923 to 1932, and served on the staffs of the Tacoma General Hospital and St. Joseph's Hospital, also of that city.

He was a member of the American Medical Association, Washington State Medical Society, and the Pierce County Medical Society. Dr. Jonez became an Associate Fellow of The American College of Allergists in 1946 and was elected to Fellowship in 1948. He was actively interested in allergy and served as instructor in the Graduate Instructional Courses in 1949, 1950, 1951, and 1952.

Members of the College will learn of his passing with regret, and, in their name, we extend our condolences to his family and friends.

ADOLPH A. LILIEN

Notice of the death of Dr. Adolph A. Lilien of New York City has been received with regret. Dr. Lilien was born January 16, 1890, in Austria and had practiced medicine for thirty-one years. He received his degree from the Vienna Medical School in 1917. He interned at the Vienna General Hospital and the University Hospital, Prague, Czechoslovakia. Postgraduate studies were continued at both of the aforementioned hospitals, and postgraduate training in allergy was received at Mt. Sinai Hospital, New York City, in 1936.

Dr. Lilien held a number of teaching posts, including those of clinical assistant, senior assistant in allergy, and associate in physical medicine at Mt. Sinai Hospital, New York City, and associate in medicine at The Sea View Hospital, New York City. He was a specialist in diseases of the chest and made many contributions to various professional journals, both in this country and abroad.

Dr. Lilien was elected to Fellowship in The American College of Allergists in 1949. He was also affiliated with the American Academy of Allergy, the New York Academy of Medicine, and the American Medical Association, as well as with state and county medical societies.

Dr. Lilien was unmarried. He enjoyed an excellent reputation among his colleagues, and will be greatly missed by his associates. We offer sympathy to the relatives who survive him and to the friends who were privileged to know him.

MORTON W. WILLIS

Word has just been received of the death of Dr. Morton W. Willis of Jamaica, New York, which occurred May 23, 1953, after a prolonged illness.

Dr. Willis was born in New York City on May 9, 1908. He was graduated from City College of New York in 1927 with a Bachelor of Science degree and from New York University Medical College in 1932. He interned at Los Angeles County Hospital and Mr. Sinai Hospital, New York City. Beginning in 1946, he served as assistant clinical professor of medicine at New York Medical College. Dr. Willis also served as director of the Department of Allergy at Jamaica Hospital. He was Associate Physician at Queens General Hospital and Jamaica Hospital, as well as senior clinical assistant, Mt. Sinai Hospital. Dr. Willis specialized in internal medicine. In 1948, he was elected Fellow of The American College of Allergists.

Dr. Willis was also affiliated with the American Medical Association, the New York State Medical Society, and the Queens County Medical Society.

His survivors include his wife, Roslyn Willis. Dr. Willis will be missed by friends and colleagues alike. Members and officers of the College extend their sincerest sympathy.

THE AMERICAN COLLEGE OF ALLERGISTS

Decennial Instructional Course and Decennial Congress
Roney Plaza Hotel, Miami Beach, Florida
April 5-10, 1954

Dr. Giles A. Koelsche, Over-All Program Chairman

The Decennial Instructional Course, April 5-7, 1954, with Dr. Ethan Allan Brown, Chairman, and Dr. Hal Davison, Co-Chairman, will have forty instructors. See the January-February "Annals of Allergy" for the complete program. You will receive a Preliminary Program the first of January. The following is an outline:

Monday morning, April 5, there will be eight lectures on the various phases of NASAL ALLERGY. Dr. Hans Selye will be guest speaker at the luncheon, and his subject will be "Stress and the Allergic Disorders." Seven lectures on THE ALLERGIC LUNG will be given in the afternoon. Evening panels, from 8 to 10 P.M., will be devoted to "The Steroid Hormones" and a Pediatric Panel.

Tuesday morning, April 6, there will be nine lectures on DERMATOLOGIC ALLERGY. Dr. Alvan Barach, guest speaker at the luncheon, will talk on "Recent Advances in Inhalational Therapy of Lung Disorders." Eight lectures on MISCELLANEOUS ALLERGIC DISORDERS will be given in the afternoon. Evening panels will be on "Antihistaminic Agents" and "Mold Allergy."

Wednesday morning, April 7, the subject will be THE ALLERGIC PATIENT. Lectures on THE ALLERGIC STATE will be given in the afternoon, and the evening session will have a panel—"Any Questions?"

The program on Psychosomatic Allergy was such an interesting feature last year, it was decided to repeat it this year. Wednesday evening there will be four seminars on EMOTIONAL FACTORS IN ALLERGIC DISORDERS. On Friday evening there will be a CLINICAL PANEL ON PSYCHOSOMATIC ALLERGY, with Dr. Hyman Miller as moderator, which will be a summary of the four seminars.

From Monday through Friday, April 5-9, from 9:00 A.M. to 5:00 P.M., Dr. Stephen D. Lockey and associates will give lectures and demonstration on OFFICE AND LABORATORY PROCEDURES.

The price of the Instructional Course is $65.00, including the three buffet luncheons.

The Decennial Congress begins Thursday morning, April 8, with the full day devoted to a General Session under the Chairmanship of Dr. Giles A. Koelsche. On Thursday noon Dr. J. Warrick Thomas will be the moderator at a round table luncheon on the subject "Pitfalls in the Diagnosis and Management of Asthma." Thursday evening will be a meeting devoted to relaxation known as "Florida Night" for which the Roney Plaza is famous. The evening will begin with a cocktail party which will be followed by an elaborate dinner out-of-doors in the Garden Patio under the swaying palms. There will be dancing under the stars in the Palm Patio.

Friday morning there will be a section on Pediatric Allergy under the Chairmanship of Dr. Jerome Glaser, followed by two round table luncheons, one on Pediatric Allergy with Dr. C. Collins-Williams presiding, and one on Otolaryngologic Allergy with Dr. Lawrence K. Gundrum presiding. On Friday afternoon Dr. John Gillaspie, Chairman, will introduce Dr. M. Murray Peshkin who will give the Presidential Address, and the guest speaker, Dr. John W. Gowan, Professor of Genetics, Iowa State College of Agriculture and Mechanic Arts, Ames, Iowa, whose subject will be "Individuality as a Factor in Resistance to Disease." A business meeting will follow for the remainder of the afternoon. The Dermatological Section, with Dr. Adolph B. Loveman presiding, will meet in the evening. Saturday morning, April 10, there will be a Section on Otolaryngology, with Dr. Hugh Kuhn presiding.

PLEASE MAKE YOUR HOTEL RESERVATION DIRECTLY TO THE HOTEL ON THE FORM SENT YOU OCTOBER 7.

For detailed information, address the Secretary-Treasurer, ACA, 401 LaSalle Building, Minneapolis 2, Minnesota.

News Items

AMERICAN ASSOCIATION OF IMMUNOLOGISTS

The 1954 meeting of the Federation will be held in Atlantic City, April 11-16, 1954. Scientific sessions will begin Tuesday, April 13, at 9:00 A.M. and continue through Friday afternoon, April 16. The headquarters hotel will be the Ambassador. Registration desks will open Monday, April 12, at 9:00 A.M. in the lobby of Convention Hall and will remain open until 10:00 P.M. on that day. Tuesday through Friday, registration desks will be open from 8:00 A.M. to 5:00 P.M. The official badge issued at the registration desks must be worn to secure admission to the scientific sessions and other activities. Industrial scientific exhibits together with those of members and institutions will be located on the Main Arena Floor at Convention Hall. Exhibits will be open from 12:00 noon until 6:00 P.M. on Monday, April 12, and from 8:45 until 5:30 on Tuesday, Wednesday and Thursday. Exhibits will close Friday, April 16, at 3:30 P.M. John Y. Sugg is Secretary, and the Convention Office is 2101 Constitution Avenue, Washington 25, D. C.

NEW ACA MEMBERS

At the last meeting the Board of Regents elected the following new Associate Members:

Dr. F. Stanley Ewing, Sinton, Texas
Dr. Emanuel Hellreich, Brooklyn, New York
Dr. Fred M. Blix, Ladoga, Indiana
Dr. Joseph H. Gillman, Brooklyn, New York
Dr. J. William Hervert, Lincoln, Nebraska
Dr. David S. Huber, Pittsburgh, Pennsylvania
Dr. Daniel M. Kraus, Denver, Colorado
Dr. T. Reed Maxson, Warrensburg, Missouri
Dr. Lamar B. Peacock, Atlanta, Georgia
Dr. Manuel A. Schofman, Miami Shores, Florida

A new Corresponding Member, also elected recently, is Dr. Fernando Dias Campos, Jr., of Porto Alegre, Rio Grande do Sul, Brazil, South America.

A hearty welcome is extended to these new College members.

ALERGIA, REVISTA IBEROAMERICANA DE ALERGOLOGIA

The new *Alergia,* Vol. 1, No. 1, August, 1953, marks the introduction of the Spanish-American journal of allergy. Director General: Dr. Mario Salazar Mallen, Mexico, D. F. Directores Asociados: Dr. Guido Ruiz Moreno, Buenos Aires, Argentina; Dr. Carlos Canseco, Jr., Monterrey, Nuevo León, Mexico. Redactores: Dr. A. E. Bachmann, Argentina, Dr. J. F. Dumm, Argentina, Dr. J. Martorelli, Argentina, Dr. Miguel A. Solari, Argentina, Dr. Ernesto Mendes, Brasil, Dr. Jose Quintero Fossas, Cuba, Dr. Plutarco Naranjo Vargas, Ecuador, Dr. J. Sánchez Cuenca, España. *Alergia* combines the publication *Alergia* (Buenos Aires, Argentina) and *Revista Mexicana de Alergologia* (Monterrey, Mexico, organ of the Mexican Society of Allergists). Please send manuscripts to Director Asociado, Dr. Guido Ruiz Moreno, Anchorena 1338, Buenos Aires, Argentina. Subscription rate $35.00 (pesos mexicanos) $4.00 (dolares) per year. Please send remittance checks to Administration Office, M. Cole de Pardo, Medellin 94, Mexico, D. F.

NOTICE: TO ALL FELLOWS OF THE AMERICAN COLLEGE OF ALLERGISTS

Pursuant to Article V, Section 7 (g) of the By-Laws, the Nominating Committee has selected one candidate for each elective office, to be voted on at the next annual election. This selection is known as the

OFFICIAL BALLOT

President-Elect ..... Lawrence J. Halpin, M.D.
First Vice President ..... George L. Waldbott, M.D.
Second Vice President ..... Rudolf L. Baer, M.D.
Secretary-Treasurer ..... Fred W. Wittich, M.D.

BOARD OF REGENTS—THREE-YEAR TERM

James A. Mansmann, M.D.
James E. Stroh, M.D.
Susan C. Dees, M.D.

ARTICLE V. *Section 7 (g).—The Nominations of Officers.*—The Nominating Committee shall be composed of five (5) members: the retiring president, two (2) members of the Board of Regents, and two (2) members of the College-at-large elected by the Board. It shall convene within twenty-four (24) hours after its selection; thereafter and not earlier than ninety (90) days but not more than six (6) months following its selection, the Nominating Committee shall select one (1) candidate for each elective office and this shall be known as the official ballot. In making its selection it shall take into consideration the qualifications, fitness, capacity, standing and accomplishments in the field of allergy of those selected. Any and all information contained in the membership records maintained in the Secretary's office as to any selectee shall, upon request, be seasonably supplied to the Committee. As soon as convenient thereafter, but not less than three (3) months before the ensuing election, notice of this official ballot shall be given to all voting Fellows of the College. This notice may be given either by publication thereof in the official organ of the College, ANNALS OF ALLERGY, or by mail.

Additional nominations may also be made by petition, signed by ten (10) Fellows and sent to the office of the Secretary-Treasurer, provided said additional nominations are received in the office of the Secretary-Treasurer at least thirty (30) days prior to the next annual meeting. Nominations may also be made from the floor at any annual meeting. The election of officers and Regents shall be by ballot and shall be by a majority of the votes cast at the annual meeting.

THE NOMINATING COMMITTEE
J. WARRICK THOMAS, M.D., *Chairman*
L. EVERETT SEYLER, M.D.
WALKER L. RUCKS, M.D.
JOHN H. MITCHELL, M.D.
HARRY L. ROGERS, M.D.

PRESENT OFFICERS

President ..... M. Murray Peshkin, M.D.
President-Elect ..... Homer E. Prince, M.D.
First Vice President ..... Mayer A. Green, M.D.
Second Vice President ..... Frank A. Simon, M.D.
Executive Vice President and Counsel ..... Eloi Bauers
Secretary-Treasurer ..... Fred W. Wittich, M.D.

BOARD OF REGENTS

	Term Expires
Harry S. Bernton, M.D.	1955
Vincent J. Derbes, M.D.	1955
Jerome Glaser, M.D.	1956
Morris A. Kaplan, M.D.	1956
Giles A. Koelsche, M.D.	1956
Hyman Miller, M.D.	1954
Bret Ratner, M.D.	1954
Walker L. Rucks, M.D.	1954
L. Everett Seyler, M.D.	1955
M. Murray Peshkin, M.D. (President)	1954

POSTGRADUATE COURSE—AMERICAN TRUDEAU SOCIETY

A postgraduate course on pulmonary function, sponsored by the American Trudeau Society in co-operation with the Massachusetts Tuberculosis and Health League, Harvard Medical School, Boston University School of Medicine and Tufts College Medical School, will be held in March, 1954, at the Boston City Hospital, Boston, Massachusetts. The course was such a success last year that it is being repeated with minor changes. The course is on The Measurement of Pulmonary Function in Health and Disease. Registration is limited. The purpose of this course is to present the fundamental concepts and methods of analysis of normal and abnormal physiology of the lungs in a manner that can be readily understood by the many physicians concerned with diseases of the chest. There will be a limited number of scholarships covering part or all expenses, available through the courtesy of the National Tuberculosis Association. The fee for the course is $50.00, payable to the Massachusetts Tuberculosis and Health League.

There are twenty-three instructors covering the following subjects: 1. Mechanical and physiologic aspects of respiration; 2. Methods of analysis of pulmonary function; 3. Cardio-pulmonary relationships; 4. Alterations of pulmonary function as a result of disease; 5. Alterations of pulmonary function as a result of therapy; 6. Clinical application of tests of pulmonary function.

Physicians accepted for this course may obtain information regarding hotel accommodations from Mr. Nelson R. Kraemer, Executive Director, Massachusetts Tuberculosis and Health League, 131 Clarendon Street, Room 802, Boston 16, Mass.

THE BRITISH ASSOCIATION OF ALLERGISTS

The General Meeting of the British Association of Allergists was held on Saturday, July 4, 1953, at Cardiff, with Dr. D. A. Williams presiding. Dr. A. W. Frankland opened the morning session with a film on "Hay Fever." Mr. H. A. Hyde presented a paper on "Further Investigations on Atmospheric Pollen," Mr. Merfyn Richards talked on "A Survey of Airborne Mould Spores," and Dr. Kate Maunsell gave a paper on "Endogenous and Exogenous Factors Leading to Fungal Sensitization." Two papers were given in the afternoon, one by Dr. Linford Rees on "The Interrelationship of Causative Factors in Asthma," and the other by Dr. J. Jacobs on "Differential Diagnosis of Asthma in Children." Dr. A. W. Frankland is Honorary Secretary.

MICHIGAN ALLERGY SOCIETY

The officers of the Michigan Allergy Society for 1953-54 are: President, Donald D. Smith, M.D., Pontiac; Vice President, Joseph H. Shaffer, M.D., Detroit; Secretary, Sidney Friedlander, M.D., Detroit. The next meeting of the Society will be held in Detroit on January 20, 1954, at which time Dr. Elvin A. Kabat, Ph.D., Professor of Microbiology, College of Physicians and Surgeons, Columbia University, New York, will address the group on "Quantitative Immunochemistry in the Study of Allergic Reactions."

THE SOUTHWEST ALLERGY FORUM

The annual meeting of the Southwest Allergy Forum will be held May 9-11, 1954, at the Roosevelt Hotel, New Orleans, Louisiana. Part of the program will consist of practical demonstrations to be held at Tulane and Louisiana State University Medical Schools and at Charity Hospital. These demonstrations will include not only clinical diagnostic procedures, but also demonstrations of gross and microscopic pathological specimens.

The Executive Committee is as follows: Dr. Henry D. Ogden, President; Dr. Vincent J. Derbes, Vice President; Dr. Stanley Cohen, Secretary; Dr. Nicholas K. Edrington, Treasurer; Dr. Jack R. Anderson, Dr. H. Whitney Boggs, Dr. W. H. Browning, Dr. B. G. Efron, Dr. A. J. McComiskey, Dr. Jack E. Strange, Dr. Narcisse F. Thiberge, and Dr. J. Dudley Youman, Jr.

NEW YORK ALLERGY SOCIETY

At the annual meeting of the New York Allergy Society, November 16, 1953, at the New York Academy of Medicine, the following officers were elected:

President—Dr. Frederick R. Brown
President-elect—Dr. William B. Sherman
Vice President—Dr. Murray Albert
Secretary—Dr. Leoni N. Claman
Treasurer—Dr. Samuel J. Prigal

All communications may be addressed to the Secretary, Leoni N. Claman, M.D., 40 East 88th St., New York 28, N. Y.

OPENINGS FOR RESIDENCY IN ALLERGY

The Medical Center, School of Medicine, University of Pittsburgh, and the United States Veterans Hospital, Pittsburgh, announce several openings for a one par residency in allergy. This includes clinical and laboratory training, as well as teaching experience. Salary at $1500 to $3300 per annum. Address inquiries to Leo H. Criep, M.D., The Bigelow, Pittsburgh 19, Pennsylvania.

MEDICAL AND HEALTH BUDGETS OF FEDERAL AGENCIES

No doubt physicians will be interested in the following data on Medical and Health budgets of Federal Agencies obtained from *The Journal of the American Medical Association,* November 14, 1953. Various departments showed the following expenditures:

DEPARTMENT OF HEALTH, EDUCATION AND WELFARE

($340,553,000 Total)

Office of Vocational Rehabilitation		$ 23,655,500
Food and Drug Administration		6,250,000
Children's Bureau		31,525,000
Bureau of Public Assistance (Medical and Health Payments)—approximately		50,000,000
Office of Surgeon General, Public Health		2,900,000
Tuberculosis Control		6,000,000
Venereal Disease Control		5,000,000
General Assistance to States		13,250,000
Communicable Disease Control (Communicable Disease Center, Atlanta, Ga.)		5,000,000
Engineering, Sanitation and Industrial Hygiene		3,162,500
Alaska—Disease and Sanitation Investigations and Control		1,082,000
Hospitals and Medical Care		33,100,000
Foreign Quarantine Service		2,900,000
National Institutes of Health (total)		71,153,000
National Cancer Inst.	20,237,000	
Mental Health Inst.	12,095,000	
National Heart Inst.	15,168,000	
Dental Health Inst.	1,740,000	
Microbiological Inst.	5,738,000	
Institute for Neurological Dis. and Blind	4,500,000	
Institute of Arthritis and Metabolic Dis.	7,000,000	
General Funds	4,675,000	
Hospital Construction Grants—Obligational Cash		65,000,000
Grants for Hospital Construction—Liquidational Cash		19,700,000
Hospital Construction Administrative Expenses		875,000

VETERANS ADMINISTRATION ($747,415,264 Total)	
Medical, Hospital and Domiciliary Administration	7,757,900
Research—Approximately	5,500,000
New Construction and Contract Liquidation	38,685,664
Supply Depot Operations—Approximately	1,350,000
Contract Hospitalization	20,583,100
Domiciliary Care	24,248,200
Outpatient Care	92,677,900
Inpatient Care	555,000,000
Medical Education and Training	1,300,000
Capital Expansion	312,500
DEPARTMENT OF DEFENSE ($533,311,000 Total)	
Army Medical Services—Approximately	$238,994,000
Naval Medical Services—Approximately	161,429,000
Air Force Medical Services—Approximately	132,801,000
Office of Assistant Secretary of Defense (Health and Medical)—Approximately	87,000
DEPARTMENT OF STATE ($14,127,733 Total)	
World Health Organization	2,993,400
Pan-American Sanitary Bureau—Approximately	1,320,000
International Children's Emergency Fund	9,814,333
DEPARTMENT OF LABOR ($8,960,000 Total)	
Bureau of Employes' Compensation—Approximately	8,500,000
Health and Safety Program—Approximately	460,000
FOREIGN OPERATIONS ADMINISTRATION ($24,500,000 Total)	
Technical Assistance Programs	24,500,000
DEPARTMENT OF INTERIOR ($27,258,600 Total)	
Bureau of Indian Affairs	21,400,000
Bureau of Mines (This money is spent for mine inspection and investigations, investigation of accidents and rescue work, and explosive testing and research)	5,060,000
Alaskan Mental Health Program	798,600
DEPARTMENT OF COMMERCE ($621,000 Total)	
Bureau of Standards—Approximately. (Tests are being made on such things as hearing aid batteries, substitutes for blood plasma, automatic blood pressure recorder, heart pump, and artificial kidney)	300,000
Civil Aeronautics Administration. (This item is for salaries and administrative expenses in carrying out the medical portion of the authority's flight safety program.)	321,000
DEPARTMENT OF TREASURY ($2,790,000 Total)	
Bureau of Narcotics	2,790,000
DEPARTMENT OF JUSTICE ($1,326,000 Total)	
Bureau of Prisons	1,326,000
INDEPENDENT OFFICES ($68,019,600 Total)	
National Science Foundation	8,000,000
Federal Civil Defense Administration—Approximately	26,650,000
Atomic Energy Commission (Medical)—Approximately	26,565,000
Health Resources Advisory Commission—Approximately	91,000
National Advisory Commission to Selective Service	265,000
Panama Canal Zone (Medical)	5,448,600
Federal Trade Commission (Med.)—Approximately	1,000,000
MISCELLANEOUS ($7,000,000 Total)	
Commission on Intergovernmental Relations	500,000
Commission on Organiz. of Executive Branch of Government	500,000
Federal Employes Health Programs—Approximately	6,000,000

BOOK REVIEWS

THE ALLERGIC PATIENT AND HIS WORLD, INCLUDING SOURCES OF ALLERGENS. By Florence Eastty Sammis, M.D., 166 pages, 12 illus. Price $4.75. Springfield, Ill.: Charles C Thomas, 1953.

This neat little volume, the outgrowth of material used originally by the author's private patients, was designed to enable the allergic patient to "co-operate intelligently" with his physician and to save the latter many time-consuming explanations.

This book deals with the major forms of allergy, such as asthma, hay fever, and allergic skin conditions. Elimination diets, special instructions, and forty-five recipes are also included. Questions and answers in allergy, the result of some twenty years' practice in this field, are an important feature of the book.

The author has taken into consideration, also, the changing pattern of allergic diseases. The sources of inhalant and ingested allergens have been brought up to date. In addition, some attention has been paid to revising the sources of chemical allergens which may act as contactants.

The section on pollens by Mr. Durham may serve the busy physician as a quick reference guide to the pollens and pollen counts of his particular area and which pollens are needed for tests and treatment.

BACTERIAL AND MYCOTIC INFECTIONS OF MAN. Edited by R. J. Dubos. 37 contributors. 2nd edition. XIV 886 pages. Price, $7.50. Philadelphia: J. B. Lippincott Co., 1953.

In comparison with the first edition of this joint venture of American microbiologists, the improvement is great indeed, both in consistency of purpose and in quality. The book now closely approaches its intention of giving a truly representative account of the medical aspects of microbiology and immunology adjusted to the approach and geared, in the selection of data, to the needs of medical students and physicians. The majority of chapters are top grade in factual reliability and critical interpretation. Technical data are largely restricted to the amount necessary for the appreciation of procedural problems. Instead, the book contains more clinical data and epidemiological features important for practical medicine than is usual in books of this kind. Of particular interest for the allergists are the chapters on serology and immunochemistry by H. P. Treffers and on the allergic state by M. W. Chase, which are about the best "teaching" presentations of these subjects available anywhere. Their careful study would amply repay the acquisition of this book for any allergist. Of special usefulness to the medical profession and nowhere else available within textbook form in similar quality are the chapters on blood groups (P. Levine), on medical mycology (N. F. Conant), on chemotherapy (B. D. Davis and W. McDermott) and on medical bacteriology (that is, the much neglected art of using available method to best advantage) by G. G. Kalz and E. D. G. Murray.

A.J.W.

VIRAL AND RICKETTSIAL INFECTIONS OF MAN. Edited by Th. M. Rivers. 30 contributors. 2nd edition. XVI 719 pages. Price, $7.50. Philadelphia: J. B. Lippincott Co., 1953.

The second edition of this splendid presentation of the medical aspects of virology vividly reflects the progress made in this field during the last five years. The increase in size of about 200 pages represents solid gain in factual knowledge. In view of the number of contributors, the quality of presentation is kept on an amazing

level of quality and also of uniformity of approach to the best possible account of what is medically important. The technical considerations are concentrated in separate chapters and—like in the bacteriological companion volume—directed toward the essentials for proper appreciation of the problems involved. For the medical man who wants to be up-to-date in this important field, this is *the* book to acquire. Thanks to the aid of the National Foundation for Infantile Paralysis, this (like the companion volume on bacteriology) is available at a very modest price.

A.J.W.

THE 1953-54 YEAR BOOK OF MEDICINE. Edited by Paul B. Beeson, M.D., Ensign Professor of Medicine and Chairman of the Department of Internal Medicine, Yale University School of Medicine; Carl Muschenheim, M.D., Associate Professor of Clinical Medicine, Cornell University Medical College; William B Castle, M.D., Professor of Medicine, Harvard University; Tinsley R. Harrison, M.D., Professor of Medicine, Medical College of Alabama, Birmingham; George B. Eusterman, M.D., Emeritus Professor of Medicine, University of Minnesota (Mayo Foundation); Robert H. Williams, M.D., Professor and Executive Officer, Department of Medicine, University of Washington. 736 pages, 127 illus. Price, $6.00. Chicago: The Year Book Publishers, Inc., 1953.

This year book is one of a series which deals with the working details of the most up-to-date diagnostic methods and treatment procedures. The editors, outstanding in their respective fields, have produced a most useful volume, written in a simple and concise style and amply illustrated with charts, graphs, and photographs.

The book is divided into six parts, dealing with infections, the chest, the blood and blood-forming organs, the heart and blood vessels, the kidney, the digestive system, and metabolism. Under infections are included discussions of Fort Bragg fever, cat scratch disease, and poliomyelitis. The section on the latter contains an evaluation of Red Cross gamma globulin as a prophylactic agent for poliomyelitis. Under the section on chest are descriptions of the use of isoniazid and its isopropyl derivative in tuberculosis therapy. Cardiac surgery and rare types of heart disease are considered under the heart.

The last part of the volume—a new addition to the year book—treats of metabolism, with sections on the adrenal, pituitary, and thyroid glands. In connection with the latter, reference is made to the new and interesting studies with triiodothyronine.

BASIC BACTERIOLOGY. ITS BIOLOGICAL AND CHEMICAL BACKGROUND. By Carl Lamanna and M. Frank Mallette. XIV 677 pages. Price, $10.00. Baltimore: The Williams & Wilkins Co., 1953.

This is a well-written and well-organized bacterial physiology textbook. For those who are interested in microbial infection and microbial synoikism—as all allergists ought to be—this is a book handy to have around when any questions come up as to what makes micro-organisms "tick,"—and similarly, when the question comes up, what makes bacteria die (see the excellent chapter on disinfection and related problems).

A.J.W.

ENZYMATIC CONCEPT OF ANAPHYLAXIS AND ALLERGY. By Z. Z. Godlowski, M.D., Ph.D. Research Fellow of the Carnegie Trust, Edinburgh. 120 pages. Price, $3.50. Edinburgh and London: E. & S. Livingstone Ltd., 1953. Baltimore: Williams & Wilkins Co., 1953.

With the growing appreciation of the role of enzymatic chemistry in the mechanism of anaphylaxis and allergy this essay is thought provoking. The author is justified in presenting his views as the result of many years of research on varied subjects which now show close relationships. Cognizant of the complicated interaction of enzymes and proteins which are influenced by numerous environmental

factors, the author, through his own work and intimate knowledge of the literature, advances a convincing concept of the mechanism of allergy and related phenomena.

In a pioneer field there necessarily is interjected some logical theorizing in an effort to correlate many diverse observations. The role of eosinophiles has always been an intriguing subject and the author's experimental work on this subject is most interesting and enables one to understand eosinophile infiltration and its function. There are excellent tables illustrating the details, and the colored figures superbly illustrate the histologic results. There are four chapters: (1) Enzymatic Concept of Anaphylaxis and Allergy; (2) Hormonal Involvement in Anaphylaxis: (3) The Role of Eosinophils in Anaphylaxis and The Fate of Eosinophils in Eosinopenia Hormonally Induced; and (4) General Conclusions.

This is not a book for the beginner but for the clinician engaged in scientific research, as well as the physiologist and the pathologist, all of whom should find this book most interesting, informative and stimulating.

ATLAS OF REGIONAL DERMATOLOGY. Ernest K. Stratton, P.D., M.D., Research Associate, The George Williams Hooper Foundation for Medical Research, University of California Medical Center, San Francisco, Calif. Contributors: Harry L. Arnold, Jr., M.D., Honolulu, Hawaii; Maurice J. Costello, M.D., New York City; and Paul Fasal, M.D., San Francisco, Calif. 288 pages, 596 illustrations (25 in color). Price, $15.00. Springfield, Ill.: Charles C Thomas, 1953.

A modern atlas of regional dermatology is welcome. All of the contributors are outstanding dermatologists. The Atlas presents regional groupings of most of the common skin diseases. There has been a careful selection of pictures involving the same disease in different locations of the body in a group which facilitates differential diagnosis. Carefully selected pictures of the various stages of the same disease are shown in each location. No attempt was made to group them according to the etiologic factors nor to those having similar types of skin lesions, although this latter consideration was used in making selections in many instances. A book intended primarily for the student needing pictures in identifying skin diseases does not include a bibliography, nor a discussion of the finer points on diagnosis and therapy. These can be obtained from standard texts on dermatology, as well as the Index Medicus for reference to current literature.

The clear, outstanding photographs bring the patient to the desk. They have been obtained from institutions with which the author has been associated in one role or another. The illustrations, including the beautiful color photographs, were selected from a large assortment primarily for their sharpness of detail. The regions grouped are: Diseases of the Scalp; Diseases of the Face and Neck, (including the Ears and Eyelids); Diseases of the Mouth (including the Lips and Tongue); Diseases Involving the Trunk (including the Axilla and Buttocks); Diseases Affecting the Arms, Forearms, Wrists and Hands; Diseases of the Nails; Diseases Affecting the Inner Thighs, Penis, Vulva, Pubic and Perianal Areas; Diseases Affecting the Thighs, Legs, Feet; Leprosy; Skin Manifestations of the Acute Infectious Diseases; and Color Reproductions of Certain Dermatoses. Under the groupings there is a brief but succinct description of the various skin diseases illustrated, including synonyms, etiology, symptoms, diagnosis and treatment. This makes the Atlas very practical and informative. Some of the photographs simulate the late Professor Max Brödel's drawings of human pathologic lesions. The paper stock and format have been excellently chosen by the publishers. There are many excellent photographs of contact dermatitis, infectious eczematoid dermatitis, drug allergies and eczemas of every description. The index has an excellent feature of listing the page as well as the picture for immediate reference.

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NEW TREATMENT FOR BRONCHIAL ASTHMA EVALUATED

Several members of the College have submitted clippings from newspapers and have asked for references in the literature concerning a new drug. One was from a Sacramento, California, daily paper, with a release from Baltimore entitled, "New Drug Gives Long Relief for Asthmatics." A letter of inquiry was sent to *The Journal of the American Medical Association,* and Dr. J. F. Hammond, Associate Editor, replied December 3, 1953:

"A copy of your letter of November 3 and the newspaper clipping which accompanied it were referred to Dr. C. F. Geschickter who has sent us the following reply: 'The cardiac difficulties in relation to emphysema and hypertension are discussed and are being published in the December issue of the *A.M.A. Archives of Internal Medicine:* Geschickter, C. F., and Popovici, A., entitled Phrenic or Post-Emphysematous Hypertension. We are enclosing a reprint of an article by Dr. C. F. Geschickter entitled 'A New Treatment for Bronchial Asthma' which appeared in *The Bulletin*—Georgetown University Medical Center, November, 1953, which may be of interest to you."

A report from the *Georgetown University Bulletin* is entitled, "A New Treatment for Bronchial Asthma, A Preliminary Report," by Charles F. Geschickter, M.D., Professor of Pathology and Director of the Department. A review of this paper will be found in the *Quarterly Review of Allergy and Applied Immunology* for December, 1953. In essence, "The new method of asthma therapy reported here represents an attempt to provide a therapeutic agent which localizes in the respiratory tissue at the site of concentration of the fixation antibodies. For this purpose, the nucleus of the quinine molecule, which is 6-methoxy-4-amino quinoline, was selected. During World War II, such quinoline compounds synthesized as antimalarials were shown to localize in both the respiratory tissue and in the reticuloendothelial structures." Wolf has previously shown that the quinine nucleus is anticholinergic and a probable bronchodilator. It would, therefore, seem likely that by adding a suitable side-chain the quinoline nucleus can also be made antihistaminic. The final compound synthesized is known as Aureoquin and the structural formula is presented. Figures showing its antihistaminic and bronchial dilator action are included. There were 155 children, fifty young adults, and eighty adults over forty years of age who received treatment by oral use of Aureoquin. There were 2.5 per cent failures in the juvenile group, 5 per cent in young adults and 10 per cent in adults over forty years of age. According to the author, about 25 per cent of the cases showed complete symptomatic remissions for periods of two to four years after therapy was discontinued. A table for dosage schedule is presented. In patients suffering from a severe acute attack, or first seen in status asthmaticus, Aureoquin therapy is supplemented by the oral or intravenous administration of a new theophylline salt, theophylline diaminopropanol.

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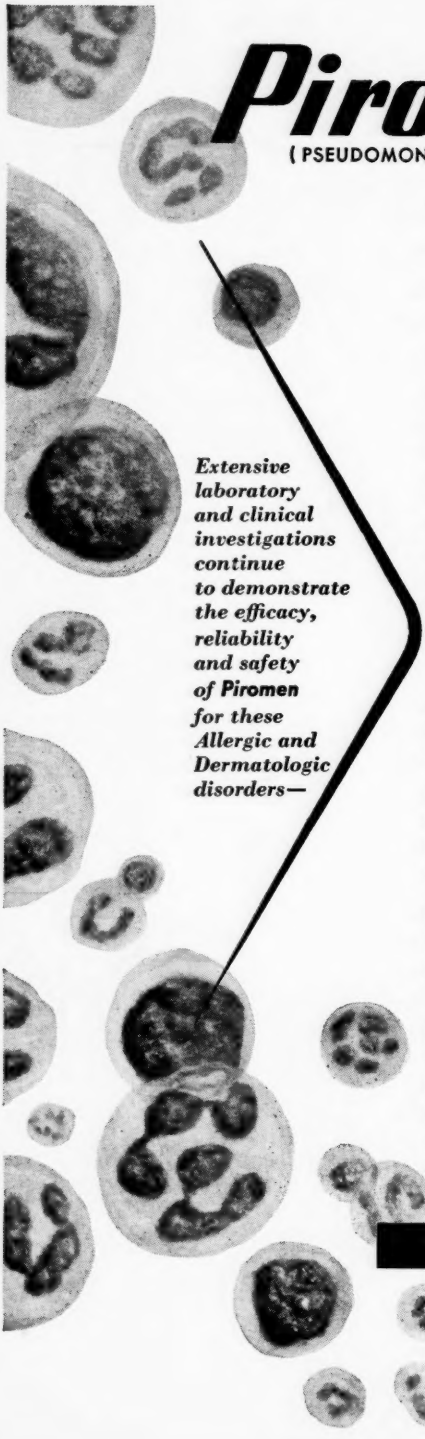

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